Cellular and Molecular Life Sciences (2021) 78:1455–1486
https://doi.org/10.1007/s00018-020-03674-w

REVIEW

Regulation of maternal–fetal metabolic communication

Caitlyn E. Bowman[1] · Zoltan Arany[1] · Michael J. Wolfgang[2]

Received: 11 June 2020 / Revised: 23 September 2020 / Accepted: 5 October 2020 / Published online: 21 October 2020
© Springer Nature Switzerland AG 2020

Abstract
Pregnancy may be the most nutritionally sensitive stage in the life cycle, and improved metabolic health during gestation and early postnatal life can reduce the risk of chronic disease in adulthood. Successful pregnancy requires coordinated metabolic, hormonal, and immunological communication. In this review, maternal–fetal metabolic communication is defined as the bidirectional communication of nutritional status and metabolic demand by various modes including circulating metabolites, endocrine molecules, and other secreted factors. Emphasis is placed on metabolites as a means of maternal–fetal communication by synthesizing findings from studies in humans, non-human primates, domestic animals, rabbits, and rodents. In this review, fetal, placental, and maternal metabolic adaptations are discussed in turn. (1) Fetal macronutrient needs are summarized in terms of the physiological adaptations in place to ensure their proper allocation. (2) Placental metabolite transport and maternal physiological adaptations during gestation, including changes in energy budget, are also discussed. (3) Maternal nutrient limitation and metabolic disorders of pregnancy serve as case studies of the dynamic nature of maternal–fetal metabolic communication. The review concludes with a summary of recent research efforts to identify metabolites, endocrine molecules, and other secreted factors that mediate this communication, with particular emphasis on serum/plasma metabolomics in humans, non-human primates, and rodents. A better understanding of maternal–fetal metabolic communication in health and disease may reveal novel biomarkers and therapeutic targets for metabolic disorders of pregnancy.

Keywords Pregnancy · Fetal metabolism · Placenta · Metabolomics · Maternal–fetal · Biomarkers

Introduction

Pregnancy may be the most nutritionally sensitive stage in the life cycle, which also means that nutritional interventions during pregnancy may have the greatest capacity to benefit maternal, fetal, and infant health. Furthermore, improved nutrition during gestation and early postnatal life may improve overall health and reduce the likelihood of chronic disease in adulthood [1, 2]. In this review, maternal–fetal metabolic communication is defined as the bidirectional communication of nutritional status and metabolic demand by various modes including circulating metabolites, endocrine molecules, and other secreted factors (Fig. 1). Maternal–fetal metabolic communication also involves a third party—the placenta—which is required for nutrient exchange in pregnant eutherian mammals and which has its own metabolic preferences. The placenta is unique in that it transiently provides the vital lifeline through which the developing fetus obtains all nutrients. While modes of placentation and placental anatomy vary greatly among eutherian mammals, this review aims to summarize findings from studies in different taxa including humans, non-human primates, domestic animals, rabbits, and rodents. Modes of metabolic communication that are conserved across species may demonstrate basic mechanisms of maternal–fetal communication that may prove helpful in modeling disorders of human pregnancy. At the same time, understanding differences in maternal–fetal communication across species can also be informative. Similarities and differences in maternal–fetal metabolic communication across taxa will be discussed throughout this review.

Maternal–fetal metabolic communication can occur by various modes (Fig. 1) that will be described; however,

✉ Michael J. Wolfgang
mwolfga1@jhmi.edu

[1] Department of Medicine, Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2] Department of Biological Chemistry, Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

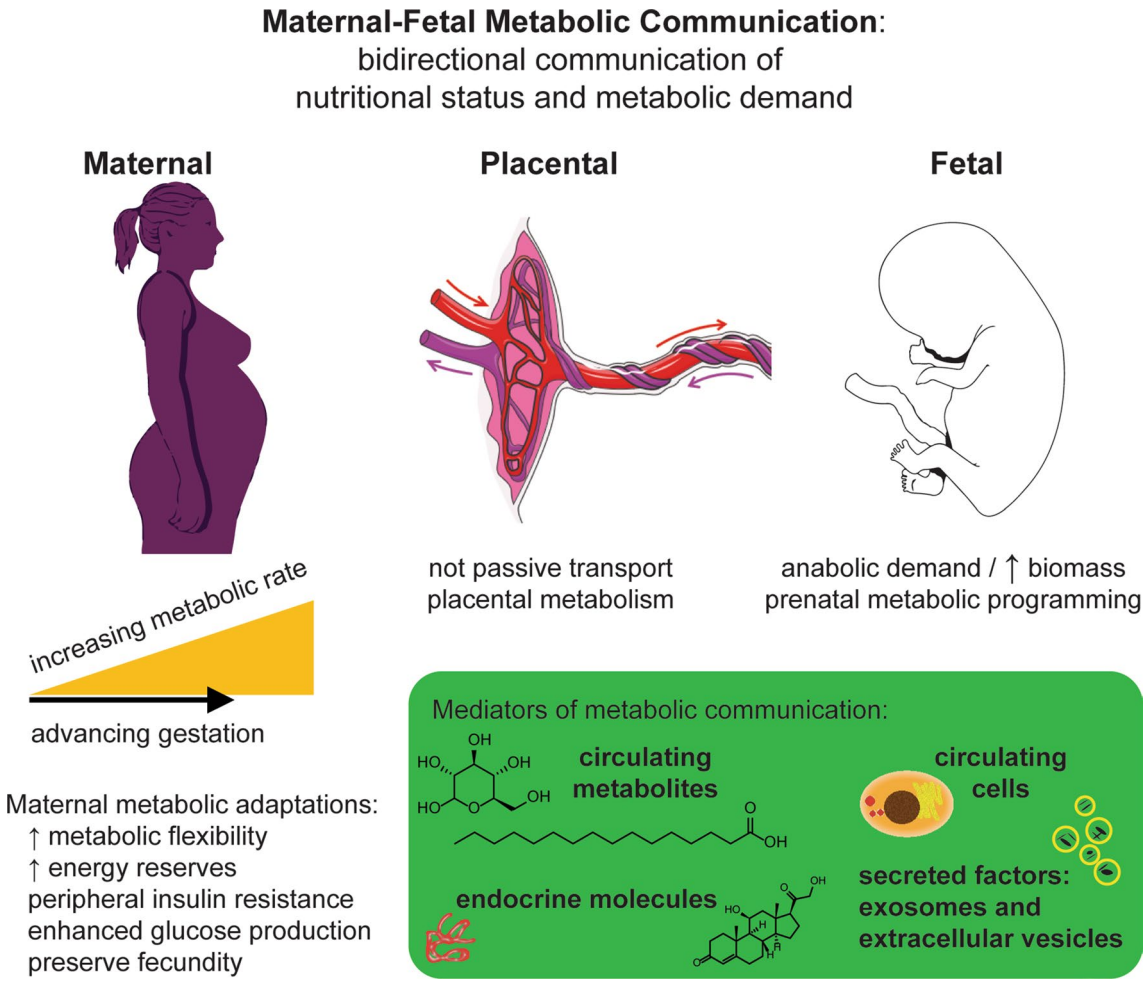

Fig. 1 Maternal–fetal metabolic communication relies on maternal, placental, and fetal adaptations. Maternal–fetal metabolic communication is the bidirectional communication of nutritional status and metabolic demand. Circulating metabolites, endocrine molecules, circulating cells, and secreted factors such as exosomes and extracellular vesicles can all contribute to this communication. Maternal metabolic adaptations include increased metabolic flexibility and building up maternal energy stores while providing nutrients to support placental/fetal growth and metabolism. Fetal metabolism is characterized by high anabolic demand, and changes in fetal metabolism during late gestation may prepare, or program, the offspring for early postnatal life

special emphasis is placed on circulating metabolites as a means of maternal–fetal communication. Maternal, placental, and fetal metabolic adaptations will be discussed in turn. First, the basic metabolic needs of the fetus will be reviewed in terms of the maternal physiological adaptations in place to ensure the proper allocation of nutrients. Maternal energy expenditure and changing metabolic demands over the course of gestation will also be discussed. Next, placental transport of key nutrients will be discussed, along with similarities or differences in placental transport among different species. Finally, maternal nutrient limitation and metabolic disorders of pregnancy will also be examined as case studies demonstrating the dynamic nature of maternal–fetal metabolic communication. The review will conclude with a summary of recent research efforts to identify metabolites, endocrine molecules, and other secreted factors that mediate maternal–fetal metabolic communication, with particular emphasis on studies in humans, non-human primates, and rodents. Altogether, a better understanding of maternal–fetal metabolic communication in health and disease may reveal novel biomarkers and therapeutic targets for metabolic disorders of pregnancy.

Maternal–fetal metabolic communication: harmony or conflict?

Successful pregnancy and parturition requires metabolic, hormonal, and immunological communication between mother and fetus [3]. The types and intensities of signals conveyed vary considerably across gestation, as do the responses elicited by these messages. Metabolic communication throughout

pregnancy is essential because a growing fetus obtains all nutrients from (and excretes all wastes to) the mother. The metabolic demands of the growing fetus, communicated by changes in metabolite concentrations or by other secreted factors, may directly modify maternal metabolism and behavior [4, 5]. Fetal metabolic demand is highest during late gestation, which is coincident with the highest basal metabolic rate and energy expenditure in pregnant women and mice [6–8].

Alterations to macronutrient metabolism during pregnancy balance the competing interests of fetal growth and maternal fecundity [9, 10]. However, the extent to which maternal–fetal communication reflects coordinated adaptations versus conflicting interests is not well understood and is likely context-dependent. For example, the competing interests of the maternally inherited and the paternally inherited genomes have resulted in some genomic regions being imprinted—that is, transcriptionally silenced or expressed from only one allele in particular tissues or at particular times in development. Importantly, of the more than 100 imprinted genes that have been identified in mice, the majority are expressed and imprinted in the placenta, the hub of hormonal communication and resource allocation during pregnancy [11–14]. In fact, even prior to implantation, environmental signals can change imprinting in a way that alters placental development and function [15, 16]. The placenta is a key regulator of fetal metabolism and it is the site where conflicts over maternal–fetal resource allocation take place. Genomic imprinting has been likened to a tug-of-war over resource allocation that would support fetal growth or maternal fecundity [17]. However, the distinction between these two seemingly opposed goals is rarely so clear-cut: Consider, for example, if additional maternal investment now will result in more vigorous offspring that will require less maternal investment later, such that the mother can begin preparing for future offspring. In fact, imprinting can have behavioral effects by altering postnatal maternal care of offspring [18]. Environmental factors can affect the expression of imprinted genes and alter nutrient availability and metabolism, but further investigations are needed to determine how metabolic state may communicate current environmental conditions to the genome/transcriptome. While a great deal of metabolic communication is necessary between mother and fetus, particularly when nutrients are limiting, fetal demands and maternal countermeasures are always at work to compromise for a balance that will suit both mother and fetus. There is both harmony and conflict under nearly all maternal–fetal interactions.

Physiological adaptations of eutherian pregnancy: placental development

Pregnancy demands a multitude of physiological adaptations that affect every organ system of the mother, and the placenta is the epitome of these adaptations as the temporary organ that mediates maternal–fetal communication and metabolite transport. Placental hormones—including growth hormone, prolactin, placental lactogens, and steroid hormones—mediate many of the maternal adaptations to pregnancy which affect multiple organ systems. A full discussion of these factors is beyond the scope of this review, but the physiological effects of placental hormones are examined in the comprehensive review by Napso et al. [19]. The placenta develops from interactions between the trophectoderm of the implanting blastocyst and the endometrium. In humans, the placenta is functionally mature by 10–12 weeks of gestation, and placental growth precedes fetal growth such that the placenta is larger than the fetus until 15–16 weeks (full term at 38 weeks) [3]. In mice, placentation begins just before mid-gestation, the definitive placenta is established at embryonic day 11, and the maximum placental volume is reached by day 16.5, as determined by stereology (parturition at day 19–20) [20, 21]. The size and transport capacity of the placenta is often indicative of fetal health and growth. Placental insufficiency is linked to miscarriage, intrauterine growth restriction (IUGR), and preeclampsia, highlighting healthy placental development as an essential physiological adaptation during pregnancy.

Interestingly, placentation has independently evolved in multiple distinct lineages. Even within the same taxonomic order, different strategies of placentation exist [22, 23]. Humans and rodents both have hemochorial placentae where maternal blood comes into direct contact with the syncytiotrophoblast, which is the first barrier to maternal–fetal exchange [24, 25]. The specialized syncytiotrophoblast has a microvillous membrane in contact with the maternal blood and a basal membrane facing the fetal blood. Humans also have a villous placental organization where each chorionic villus is composed of (1) an epithelial layer derived from syncytiotrophoblast and cytotrophoblasts and (2) an inner vascular network (including fetal vessels) and connective tissue stroma derived from embryonic mesoderm [3, 20]. Invasive endovascular trophoblasts remodel the uterine spiral arteries and replace maternal endothelium such that maternal blood flows directly around the terminal villi [20, 25]. This villous organization maximizes the surface area available for exchange. For excellent illustrations of these structures, the reader is directed to reviews by Rossant and Cross, and Silva and Serakides [20, 24].

Although the discoid, hemochorial placentae of humans and rodents have similar forms, rodent placenta lacks the well-defined villous structures of human placenta. Instead, in rodents, maternal blood bathes branching structures in a region called the placental labyrinth where most nutrient and gas exchange occurs [25, 26]. The rodent structures analogous to human chorionic villi have a trichorial arrangement with two layers of syncytiotrophoblast in contact with fetal endothelium and a cytotrophoblast cell layer in contact with

maternal blood [20, 24]. The rodent placenta also has a junctional zone which serves an endocrine function, comprised of spongiotrophoblasts and glycogen cells [25]. Glycogen cells also have the capacity to invade the maternal decidua, akin to human interstitial extravillous trophoblasts which invade uterine spiral arteries [20, 24]. The multinucleated giant cells of the outer layer of the rodent placenta are also somewhat analogous to the extravillous trophoblasts that invade the maternal spiral arteries in humans [24]. Despite subtle differences in cell types and organization, the structures of rodent and human placentae are more similar than certain other modes of placentation among eutherian mammals. A comparison of several model organisms for the study of placental development and function highlights the advantages and limitations of using these models as they relate to human placentation and parturition [27].

The hemochorial placentae of humans and rodents are the most invasive forms of placentation, as fetal tissues are in direct contact with maternal blood [23]. In the endotheliochorial placenta, maternal blood vessels are adjacent to fetal tissues but separated by maternal endothelium. In the least invasive type of placenta, the epitheliochorial placenta, maternal blood and fetal tissues are separated by maternal endothelium, connective tissue, and epithelia, which provides considerably more membranes across which nutrients must be transported to reach the fetal compartment [23]. Species with the least invasive mode of placentation include sheep, which is an important consideration when comparing studies of fetal sheep metabolism to other species. For instance, that sheep have the least invasive form of placentation while rodents and rabbits have the most invasive form may help explain some of the discrepancies in placental fatty acid transport capacity observed across species [28, 29], which will be discussed in detail in subsequent sections.

A final point of interest about comparative placentation is the reproductive strategy employed by marsupials—the other lineage of mammals that gives birth to live young. Marsupials have more anatomically simple placentae and give birth to young at a much earlier stage of development than eutherian mammals. Lactation, therefore, plays a greater role in marsupial development, emulating later stages of eutherian in utero development [30]. Marsupials have a more complex milk repertoire than eutherians, and some classes of genes expressed by marsupial mammary gland are shared with eutherian placenta and eutherian mammary gland while others are only shared with eutherian placenta [31]. Among these genes are nutrient transporters and transcriptional regulators known to be important in eutherian placenta which are conserved by their expression in marsupial mammary gland [31]. Compared to other mammals, marsupials may transmit similar signals of maternal-offspring metabolic communication, but they do so by very different means—namely, via milk instead of maternal circulation. Understanding why these signals are conserved across taxa may define key regulatory nodes for mammalian development, especially in tissues like brain that undergo robust developmental changes. Altogether, mammals have a diverse array of strategies related to placental invasiveness, degree of maturity at parturition, and early postnatal nutritional approaches to ensure offspring health and manage the energetic costs of pregnancy and lactation.

Additional physiological adaptations of pregnancy: glucose, oxygen, and metabolic flexibility

Canonically, glucose is the principal substrate driving fetal growth and energy metabolism [32]. Many maternal metabolic adaptations, as summarized in Fig. 2, ensure sufficient glucose delivery to the fetus by rendering the mother's tissues transiently insulin resistant and by enhancing maternal glucose production by 30% from early to late pregnancy [33]. Concomitant with this, blood flow to the uterus increases to 25% of cardiac output to ensure substrate and oxygen availability for mitochondrial oxidative metabolism [34]. The lumen diameter of the uterine artery expands by hypertrophic and hyperplastic growth of vascular smooth muscle cells to mediate this increased blood flow [35, 36]. The rate of umbilical flow of fetal blood to the placenta is approximately proportional to fetal weight and gestational age. Due to the villous organization of the human placenta, the total surface area available for exchange during late pregnancy is 10–15 m^2, which is the approximate area of a typical parking space [37].

Interestingly, in polytocous species such as mice, there are differences in uterine blood flow rates based on fetal position in the uterine horn. Recent microcomputed tomography and in vivo magnetic resonance imaging studies have characterized uteroplacental vascular remodeling during mouse pregnancy [38, 39]. Each placenta is nourished by branches from both the uterine artery and the uterine branch of the ovarian artery to enhance blood flow to each conceptus [40]; however, there are twofold lower uteroplacental blood flow rates in middle positions compared to ovary/cervix positions [41]. Studies from a crowded uterine horn mouse model demonstrate the effect of uteroplacental blood flow on fetal outcomes [39, 42]. Mice mated after a unilateral ovariectomy will gestate a normal-sized litter in a crowded uterine horn, in which there is a fourfold difference in blood flow to offspring from the same pregnancy [42]. Fetuses in the middle positions between the ovary and the cervix experienced the lowest perfusion pressure [41], and the smallest 5% of offspring were half the weight of the largest 5% of offspring from this crowded uterine horn model [42]. The smallest

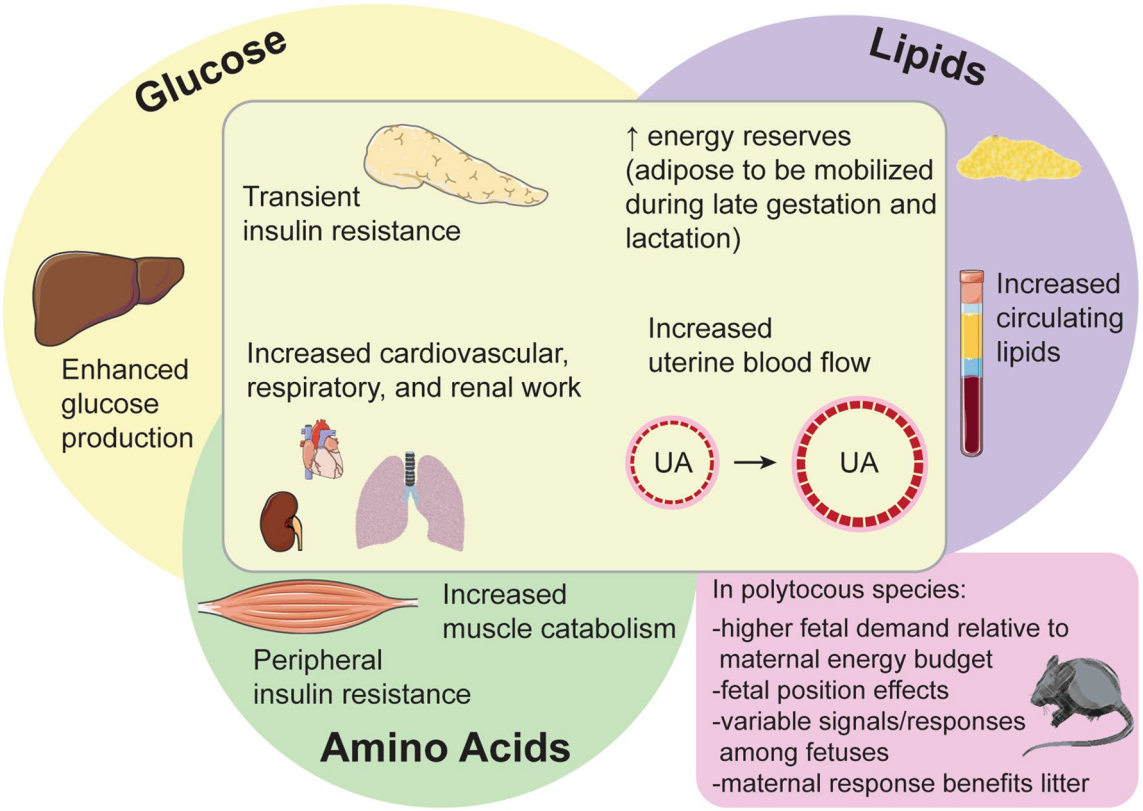

Fig. 2 Maternal metabolic adaptations. Physiological adaptations during pregnancy ensure adequate nutrient delivery to the developing fetus. Adaptations affect whole-body metabolism of glucose, lipids, and amino acids. Polytocous species have the additional challenges of higher fetal demand relative to maternal energy budget and differences in uterine blood flow based on fetal position in the uterine horn. *UA* uterine artery

pups exhibited dramatic catch-up growth over the first 3 weeks of postnatal life, and by adulthood, both intrauterine growth-restricted male mice and macrosomic male mice weighed significantly more than littermates born at median birth weights [42]. This rodent model of postnatal "catch up" growth is consistent with human epidemiological studies demonstrating that both fetal undernutrition and overnutrition can result in similar adverse metabolic outcomes in adulthood, although the mechanisms behind these outcomes are likely different. This will be discussed in further detail in "Maternal–fetal metabolic communication in nutrient stress". Polytocous species have the additional challenge of meeting the metabolic demands of several fetuses that may be competing against one another for maternal resources. Each fetus may communicate differently about metabolic demand due to genetic variations, uterine position effects, or other factors that may not be pertinent in singleton pregnancies. The maternal response must benefit the litter without compromising future fecundity. Studying variability within the same litter in polytocous species may provide insight into fetal autonomous responses to maternal metabolic communication.

In many species, another remarkable physiological adaptation of pregnancy is greater metabolic flexibility than in the non-pregnant state to protect fetal growth from acute maternal nutrient deprivation [1]. One way in which the pregnant woman is poised to provide this metabolic plasticity is through increased adipose tissue lipolysis and re-esterification, even in the fed state [43, 44]. Maternal circulating lipids (triglyceride, free fatty acids, and phospholipids) increase throughout gestation [37, 45] and are mobilized from adipose depots established during early pregnancy [44, 46]. Circulating lipids are further elevated by fasting and are available for placental transport [37, 45]. Increases in maternal circulating lipids across gestation have also been observed in rats [43, 47], mice [48, 49], guinea pigs [50], sheep [51], and non-human primates [52]. In contrast to these findings, studies of pregnant rabbits [53, 54] and some studies of pregnant ewes [55] have demonstrated unchanged or lowered maternal circulating lipids across gestation. Studies in rodents suggest that fetal uptake of lipids (and catabolic products such as ketone bodies) may be particularly important during prolonged maternal nutrient deprivation [32, 48]. The extent to which fetal tissues rely upon lipids

for energy metabolism is not well understood, but the early postnatal switch in nutrition from glucose in utero to lipid-rich milk suggests that late-gestation fetal tissues may have the capacity to utilize maternally derived lipids [56]. In this way, the metabolic plasticity of the mother may affect the fetal response to maternal nutrient deprivation.

Metabolic demands of pregnancy

Human weight increases 6 billion times over the course of prenatal life [57]. As such, it is understandable how dramatically fetal metabolic demands must change over the course of gestation. Similarly, maternal energy expenditure also increases during gestation, but it is unclear if this increase is simply proportional to increased tissue mass and food intake [58]. Longitudinal studies of energy expenditure and body composition have attempted to address this to better understand the metabolic costs of pregnancy.

Primate reproduction is characterized by a slow rate of growth over a long gestation which results in a lower nutritional stress per unit time than what is observed in species with faster generation times [1]. Interestingly, there is greater variation among mammals in birth weight than there is in terms of length of gestation; therefore, there are vast differences in rates of fetal growth across species [57]. Fetal growth rates are not linear but growth accelerates as gestation advances. In humans, birth occurs on the steepest part of the growth curve, while in rodents, for example, the greatest rates of growth occur in the first 2 weeks of postnatal life [57], even though fetal rats exhibit a 25–30% increase in weight in the last day of gestation [59]. Due to the slow rate of growth of humans, the daily energy stress of human pregnancy relative to maternal body size is lower than for most other mammals [1]. Species with higher metabolic demands during pregnancy must meet that need through substantial increases in food intake, whereas humans, with a lower nutritional stress per unit time, may instate metabolic adaptations to protect fetal growth from adverse circumstances such as food shortages. Higher gestational metabolic demand is especially apparent in polytocous species, and placental structural remodeling and changes in endocrine output likely contribute to meeting the higher maternal, placental, and fetal metabolic demands during late gestation.

In healthy human pregnancies, the average maternal weight gain is 12.5 kg (28 lbs) over the course of gestation [46]. Fetal weight may account for 25% of the weight gained in a well-nourished human pregnancy, but up to 60% in suboptimal nutritional conditions [1]. Calculations of the human energy budget during pregnancy suggests there are three ways in which energy is used: (1) energy deposited as new tissue (conceptus, amniotic fluid, uterus, breast tissue, increased blood volume) (~ 20 MJ); (2) energy deposited as maternal and fetal fat (~ 150 MJ); and (3) energy required to maintain the new tissue (~ 150 MJ) [1]. There are vast differences in energy budgets during pregnancy depending on maternal and pre-pregnancy nutrition. When maternal resources are limited, energy deposition as fat is the metabolic fate that gets re-routed. Pair-feeding of pregnant mice based on non-pregnant controls revealed no reduction in fetal body weights from pregnancies fed ad libitum; however, there was a significant reduction in maternal body weight, suggesting that maternal hyperphagia in later rodent gestation fuels adipose deposition that is particularly important during lactation [60]. In humans, maternal adipose deposition occurs in the first trimester, and it is these adipose stores that will be mobilized during late gestation to promote fetal fat accretion [37, 46]. Fat accounts for 16% of birth weight in humans, but only 1–2% in mice and rats [57]. Furthermore, this late-gestation increase in adiposity is unique to humans as most other mammals, including primates, are born lean [32, 56]. The higher adiposity of human newborns is proposed to be important for supporting the unique metabolic demands of human brain development [61]. Some species, such as rabbits and guinea pigs, accumulate fat in their livers just prior to birth, and it is these hepatic stores rather than adipose depots that are of principal importance for early postnatal metabolic adaptation in these species [29, 56].

In small mammals such as rodents, fetal mass may account for 30% of maternal body weight, hence certain metabolic adaptations may, out of necessity, increase energetic efficiency over what is observed in human pregnancy [62]. In sheep, fetal body weights are 8% of maternal body weight, which may make them a better model for fetal growth trajectories in human pregnancy [62], although there are fundamental differences in placental morphology between humans and sheep, as described above. The gold standard for assessing changes in bioenergetic demand during pregnancy is to collect longitudinal data on metabolic rates; however, it can be challenging to recruit and study a sufficiently sized cohort since there is often considerable variation among women [63]. Several longitudinal studies of pregnant women have demonstrated increasing energy expenditure across gestation by indirect calorimetry measurements [6, 7, 64, 65]. Women with a normal BMI displayed a 28% increase in basal metabolic rate (BMR, kcal/day) and a 13% increase in total energy expenditure (sum of BMR, activity energy expenditure, and thermic effect of food) from pre-pregnancy to 36 weeks gestation [6]. There is considerable variability in total energy expenditure (TEE)—some women have a net negative difference in TEE across the course of pregnancy—and this suggests that pregnant women use a diverse array of strategies to meet the metabolic demands of pregnancy [7]. Therefore, a single recommendation for increased energy intake during pregnancy is likely not applicable to all women. A longitudinal study reported that average energy

intake increased 9% from pre-pregnancy to the third trimester; however, some women had no increase in energy intake during pregnancy [7]. In addition, a study of early- and late-gestation pregnant women found no difference in postprandial energy expenditure compared to non-pregnant controls, suggesting that there are no significant alterations in efficiency of energy extraction from dietary sources [62]. This is consistent with the studies of pair-fed mice in which reducing maternal food intake was still sufficient to meet the biosynthetic and bioenergetic needs of the developing fetus [60]. While human nutrition varies greatly between and within populations around the world, the adaptive measures that protect against nutritional deficiency in utero can promote the birth of healthy human newborns in any population.

Another obstacle in studies of the energetic requirements of pregnancy, particularly in laboratory model organisms, is the challenge of accounting for fetal metabolic rate in a system where fetal mass may account for up to 30% of maternal weight. Measurements by indirect calorimetry in newborn mice suggest that metabolic rate relative to fetal body weight is likely 30% lower than the metabolic rate of the maternal body, such that maternal changes in energy expenditure account for the bulk of the increase in metabolic rate during pregnancy [8]. In addition, in a mouse model in which placentae persist after fetuses are rendered inviable during late gestation (gestational day 15), increased metabolic rate was still observed [8]. This suggests that hormonal contributions from placenta, rather than fetal demand per se, may contribute significantly to the increase in metabolic rate across gestation. In rats, as in humans, energy expenditure was 10% higher than non-pregnant values at the peak of energy expenditure just prior to parturition [58]. A recent study in mice demonstrated a decrease in late-gestation core body temperature that was reversed with high-fat feeding [66]. Altogether, the increased basal metabolic rate during pregnancy can be attributed to the combined effects of increased tissue mass, accelerated tissue synthesis, and increased cardiovascular, respiratory, and renal work [63].

Placental nutrient transport: carbohydrates

While an essential function of the placenta is nutrient and waste transport, the metabolites transferred are themselves a fundamental mode of maternal–fetal metabolic communication. Placental structure maximizes the surface area available for exchange of membrane-permeable molecules as well as ions and polar molecules which require transporter-mediated movement across cellular membranes. The developing fetus is in a constant anabolic state, increasing biomass with substrates delivered from the mother. Canonically, glucose drives fetal growth [32]. In addition to carbohydrates, amino acids and lipids are also required for fetal growth. While some of these molecules can be synthesized by the fetus, others are essential and must be supplied from the mother. Some of the key classes of nutrients provided for fetal growth will be surveyed here: carbohydrates, amino acids, lipids, and essential nutrients. Their transport and metabolic fates will be reviewed in the following sections.

Glucose and oxygen are arguably the two most important molecules transferred from mother to fetus during pregnancy. Pyruvate is the end-product of glycolysis, and pyruvate can be converted to lactate to regenerate NAD^+, a necessary cofactor for glycolysis. Oxygen, glucose, and lactate all converge at the transport and metabolism of pyruvate in mitochondria. Pyruvate can be catabolized or used for anabolic processes. While oxygen tension in utero is low relative to atmospheric levels, measurement of oxygen consumption and lactate uptake in fetal lamb provided evidence that the fetus is a net consumer rather than producer of lactate [32]. Consistent with this, fetal myocardium consumes a large amount of lactate in addition to glucose, indicating that oxidative metabolism of carbohydrate is an important energy source in developing heart [67, 68]. In addition, lactate utilization is high in neonatal brain, and the capacity for lactate import is higher in neonatal brain than in adult [69, 70]. Furthermore, recent studies revealed significant lactate utilization in adult tissues, suggesting that circulating lactate is an important oxidizable substrate in mammals [71, 72]. Together with genetic loss-of-function models in mice, these observations provide evidence for the importance of mitochondrial oxidative metabolism of carbohydrates in mammalian development [73–77]. In addition, mitochondrial metabolism regulates transitions between fed and fasted states to promote metabolic flexibility and capitalize on current nutrient availability while anticipating future nutrient limitation [78].

The predominant glucose transporter expressed in placenta is GLUT1, which promotes facilitated glucose transport with no co-transport or energy requirement. GLUT1 is found on both the microvillous and basal membranes of the syncytiotrophoblast [79]. GLUT3 can be found in the vascular endothelium where it likely enhances transplacental uptake of glucose [79]. In rodents and sheep, GLUT3 is expressed by the placenta and increases as gestation progresses. The expression of this high affinity glucose transporter may augment glucose uptake in species with a faster rate of in utero growth and a higher daily energy stress of pregnancy than humans [79]. Interestingly, placental GLUT1 expression has been found to be increased in gestational diabetes mellitus (GDM). Normally, there is more GLUT1 expression on the microvillous membrane than on the basal membrane, but in GDM pregnancies, there is increased expression of GLUT1 on the basal membrane which could promote elevated glucose transport to the fetus [79, 80]. It is unclear whether maternal or fetal factors

mediate this increase in GLUT1 expression in GDM, but it has been suggested that fetal hyperglycemia and increased insulin-like growth factor 1 (IGF-1) expression could result in elevated glucose transporter expression [81]. Interestingly, expression of the insulin receptor itself changes during placental development. During early gestation, insulin receptors are expressed on the microvillous membrane of the syncytiotrophoblast, but at term insulin receptor expression is enriched on the endothelium [82]. This change in insulin receptor expression suggests a shift from maternal regulation of insulin-dependent processes in the placenta at the beginning of gestation to fetal regulation by the end of gestation [82]. Gestational changes in plasma glucose and insulin as well as altered expression of glucose transporters and insulin receptor are carefully balanced for fetal growth and maternal health: maladaptive changes may contribute to the pathophysiology of GDM.

It is unclear exactly how glucose is made available for transport across the basal membrane of the syncytiotrophoblast since hexokinase will readily phosphorylate glucose transported across the maternal microvillous membrane. There are a few reports of glucose-6-phosphatase expression in the endoplasmic reticulum of the syncytiotrophoblast, and that may represent one path by which glucose can be transferred to the fetal side [83, 84]. Some reports even provide evidence for glucose production by the placenta, but the capacity for and regulation of this potential source of increased glucose production during late gestation is not well understood and would still require glucose-6-phosphatase [84, 85]. In one study, women undergoing elective cesarean delivery at term (after a 10 h fast) were administered deuterated glucose, and the label was found to be diluted in the umbilical vein with no further dilution in the umbilical artery, suggesting a uteroplacental source of this glucose rather than a fetal contribution [85]. Glycogen stores are another potential source of glucose available for placental use or transport to the fetus. While glycogen stores have been observed in multiple cell types in human and rodent placentae, the functions of these stores and their role in normal physiology and pathogenesis are poorly understood and may vary across gestation [86, 87]. Fetal liver glycogen could be another important source for endogenous glucose availability during a time of nutritional challenge. Glycogen stores accumulate during the last weeks before birth in humans and are critical for the first hours of postnatal life when hormonal signals such as glucagon promote glucose mobilization from these glycogen stores before the neonate consumes any milk [56, 57]. In this way, both placenta and fetal liver participate in ensuring glucose availability in late gestational life.

The placenta not only transports glucose to the fetus but it also catabolizes glucose, and recent studies challenge the widely held notion that fetal metabolism relies heavily on glycolysis. Umbilical uptake of oxygen and glucose was found to be 45% and 75% lower, respectively, than the total uterine uptake in sheep, suggesting significant glucose oxidation by the placenta [88]. In an ovine model of impaired placental growth, oxidative metabolism of glucose by placenta was impaired, but lactate efflux to the umbilical vein was increased and fetal lactate consumption increased as a result [89]. In late gestation, maternal gluconeogenesis is elevated to ensure adequate glucose supply to the fetal compartment, and lactate is an important gluconeogenic substrate. However, only 40–50% of lactate was used for gluconeogenesis in late-gestation pregnant rats, as compared to 70–80% in non-pregnant rats, suggesting that fetal utilization of lactate may account for the difference [59]. Studies in fetal lamb confirm that lactate concentrations are higher in fetal umbilical vein than in fetal artery, again consistent with the fetus being a net consumer of lactate [90]. Recent magnetic resonance imaging studies using hyperpolarized [1-^{13}C]pyruvate administered to late-gestation pregnant rats resulted in clear placental localization of signal as well as evidence of conversion to [1-^{13}C]lactate and [1-^{13}C]alanine in maternal organs and in placenta. Importantly, the intensity of the [1-^{13}C]lactate signal from placenta was lower in a rat model of preeclampsia, and this reduction in signal is not due to changes in placental perfusion but rather likely represents impaired placental metabolism of pyruvate [91]. Together, these observations challenge the dogma that in utero development is characterized by low oxygen tension and is not conducive to mitochondrial oxidative metabolism. While this may be true during early development, once placental exchange function is developed and fetoplacental mitochondrial biogenesis accelerates [73, 92], the fetus and placenta are poised to utilize oxidative metabolism for energy production and anabolism. Mitochondrial content increases in fetal tissues during development. In the placenta, zonal and age-related differences in mitochondrial oxidative metabolic function have been characterized and are sensitive to environmental cues such as oxygen concentration [92]. Nutrient availability likely also regulates mitochondrial function in the conceptus. In this way, maternal provision of nutrients may promote development of the fetal pathways necessary to utilize these nutrients [93, 94].

The process by which fetal, neonatal, and adolescent tissues develop the enzymatic functions of adult tissues has been termed “enzymic differentiation” [93], and metabolic and hormonal signals (for example, glucocorticoids) likely contribute to this differentiation [95, 96] (Fig. 3). The capacity for gluconeogenesis is acquired in the early postnatal period after glucagon stimulus, but the postnatal glucogenic response likely represents a point along a continuum of developing this capacity. Supporting this, in a non-human primate model, premature baboons had reduced endogenous glucose production compared with controls born at term

[97]. Furthermore, in a non-human primate model of maternal obesity by western diet, fetal liver gluconeogenesis was activated early [98], suggesting that signals that normally promote healthy liver enzyme development were activated prematurely, with consequences for fetal health.

Placental nutrient transport: amino acids

Amino acids can be utilized for protein synthesis and biomass accumulation as well as for energy production and synthesis of other metabolites. In contrast to glucose utilization by placenta, similar rates of uterine and umbilical uptake of amino acids were measured in sheep, suggesting that amino acids are preferentially transferred to the late-gestation fetus [88]. In humans, fetal umbilical vein concentrations of amino acids were higher than maternal circulating levels [99], and late-gestation fetal rat plasma amino acids were elevated compared to maternal plasma [100]. In addition, maternal circulating levels of certain amino acids decrease over the course of gestation [101, 102]. A thorough catalog of placental amino acid transporters is beyond the scope of this survey, but the reader is directed to these excellent reviews [26, 103–107] and a comprehensive model of integrated placental amino acid transport (since some amino acids are accumulated against a concentration gradient and others are used in concert with exchangers/antiporters that will swap one amino acid for another across a membrane) [108]. Impaired placental amino acid transport has been observed in intrauterine growth restriction (IUGR), and there was decreased activation of the key signaling hub in cellular metabolism and growth called mTOR (mammalian target of rapamycin) in IUGR placentae, indicative of impaired nutrient sensing relative to healthy placentae [109]. Hyperpolarized ^{13}C magnetic resonance imaging has been used to visualize [1-^{13}C]alanine and ^{13}C-urea in vivo in rat placenta. Urea was demonstrated to cross the placenta and reach fetal liver, although the physiologically relevant direction of urea transport is from fetus to placenta as a waste product [91]. A similar imaging approach in pregnant women could possibly be used to test for placental dysfunction that is characteristic of complications such as IUGR and preeclampsia.

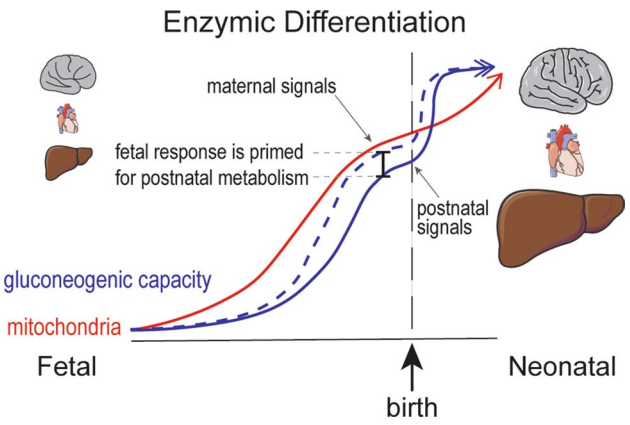

Fig. 3 Enzymic differentiation is the process by which fetal, neonatal, and adolescent tissues develop the enzymatic functions of adult tissues [93]. Shown here is a schematic representation of the transition from fetal to early postnatal metabolism. Mitochondrial content, represented in red, increases in brain, heart, and liver over this period of development. As an example, the capacity for gluconeogenesis is represented in blue and increases during late fetal development with a robust increase after birth (due to postnatal metabolic and hormonal signals). In utero nutritional stress, communicated via maternal circulating factors, may cause the fetal portion of the curve to be activated prematurely and shifted left, as shown by the dashed blue line. Both fetal under- and overnutrition have been posited to prime fetal liver metabolism for the postnatal transition [48, 98]. A similar trend could be shown for other metabolic processes that increase postnatally, such as fatty acid oxidation in the heart

Crosstalk between glucose and amino acid metabolism can promote the synthesis of non-essential amino acids from intermediates from glycolysis and the tricarboxylic acid (TCA) cycle. In addition, certain amino acids can contribute to gluconeogenesis. Although the contribution of fetal liver gluconeogenesis in vivo is unknown, fetal rat liver from severely fasted dams demonstrated increased activity of gluconeogenic enzymes and increased conversion of gluconeogenic substrates to glucose by tissue explants [100] and in response to glucagon administration in vivo [110]. Increased hepatic amino acid uptake was associated with increased fetal hepatic glucose output in insulin-induced maternal hypoglycemia in sheep [111]. A uteroplacental source of glucose during fasting in late-term pregnant women has also been suggested based on umbilical vein and artery blood glucose measurements [85]. The enhanced gluconeogenic potential prior to birth provides evidence for a strong demand for glucose to fuel energy production at the cost of promoting growth because fetal weight was decreased with prolonged maternal fasting in rats [100]. A protein-restricted diet in pregnant non-human primates did not alter offspring growth, but postnatal bone development was negatively affected by prenatal protein restriction, demonstrating that amino acid availability affects multiple organ systems [112]. Amino acid availability and pro-growth hormonal signals regulate fetal growth, and crosstalk with other metabolic pathways can affect oxidative metabolism.

Placental nutrient transport: lipids

Lipids are an important class of molecules for cellular biosynthesis, biomass accretion, energy production, and signaling purposes during fetal development. The fetus is capable of de novo lipogenesis from precursors derived from the TCA cycle. Due to the predominance of glucose as a metabolic substrate in utero, much of the carbon available for

lipogenesis likely derives from glucose. In mouse, whole-body deletion of acetyl-CoA carboxylase 1 is embryonic lethal by day 8.5, and whole-body deletion of fatty acid synthase results in pre-implantation embryonic lethality [113, 114]. Remarkably, mice with liver-specific deletion of these essential enzymes in lipogenesis develop normally and are not phenotypic when dietary fat is available, suggesting that, even in utero, liver fatty acid synthesis is not essential under normal dietary conditions [115, 116]. De novo lipogenesis has been measured in fetal rat by the incorporation of $^{3}H_2O$ into the lipid fraction. From embryonic day 17 to 20 in rats, there was a threefold increase in fatty acid synthesis; however, this study failed to provide fetal tissue-specific resolution as to where these lipids were accumulating, although it was reported that fetal liver triglyceride content accounted for 20% of total fetal triglyceride content [117]. The same study also compared exogenous uptake of [^{14}C]oleate, but the relative contributions of lipogenesis vs lipid uptake to total tissue lipid accretion cannot be determined from these labeling experiments. Glucose-derived lipogenesis is likely of greater significance in species with limited fatty acid transport across the placenta, such as species with epitheliochorial placentae like sheep and cows. Although the relative contribution of de novo synthesized lipid vs placental uptake of lipid is not well established, the importance of lipid accretion during late gestation cannot be contested. Human fetal liver accumulates 51 mg fatty acid per week from 22 weeks of gestation to term [118]. Much of this lipid is maternally derived from maternal adipose depots that are mobilized in late gestation [44, 46]. The way maternal lipids are made available for placental/fetal uptake may communicate maternal nutritional status and may affect fetal utilization [119]. The availability of lipids important for fetal development is further discussed in "Essential Nutrients".

While some studies have suggested that rates of placental transfer of lipids (particularly in species with epitheliochorial placentae) are quite low, it is important to consider that cumulative lipid transfer and accumulation in fetal tissues may be highly significant even if rates of transfer are slow. During late gestation, maternal non-esterified fatty acid (NEFA) concentrations are elevated, but circulating triglyceride (TG) levels are increased even more dramatically, such that levels are 250% higher than levels in non-pregnant women [37]. These concentrations are more than twofold higher than the postprandial peak in TG after a high-fat meal. It is largely accepted that maternal circulating triglycerides do not cross the placenta intact, yet the acyl content of TG is available for fetal accumulation [5]. In humans, for example, a TG emulsion administered to pregnant women near term was able to cross the placenta as evidenced by increased fetal arterio-venous lipid concentrations and by the observation that fetal circulating NEFA and TG fatty acid composition resembled the composition of the TG emulsion that was administered to the mother [120]. Despite this, some discrepancies in placental fatty acid transport capacity have been observed across species. In sheep, fetal blood concentrations of both free fatty acids and ketone bodies remain low relative to maternal concentrations, even upon maternal nutrient deprivation [32]. Consistent with this, radiolabeled palmitate was found to be transported poorly across the sheep placenta; however, circulating free fatty acid levels in newborn sheep were rapidly increased from 10 to 80% of maternal levels within an hour after birth [28]. In rabbits, on the other hand, maternal fasting nearly doubled fetal fat storage in both adipose and liver [29]. In this regard, the most invasive (hemochorial) placenta, as in humans, rodents, and rabbits, may allow for greatest lipid transport from mother to fetus. A potentially confounding factor is digestive differences between species with highly invasive vs less invasive modes of placentation. For instance, ruminants like sheep and cattle have the least invasive placentae and a greater dependence on gut-derived short-chain fatty acids. Species with the most invasive (hemochorial) placentae that exhibit higher capacity for long-chain fatty acid transport also tend to exhibit faster rates of prenatal brain growth and higher ratios of brain mass to body mass in both neonates and adult animals [22]. In humans, for example, the brain of a newborn weighs 25% the weight of an adult brain, but the body weighs only 5% of the adult body weight [57]. A study of brain–body allometry across eutherian mammals demonstrated patterns of faster prenatal brain growth and slower prenatal body growth among species with more invasive forms of placentation [22]. This suggests that, in these species, nutrients essential for brain growth and development (such as essential fatty acids) are made more readily available to the fetus earlier in life. Species with less invasive placentation may primarily provide these nutrients postnatally via milk. Different modes of placentation may reflect life history traits such as nutrition and offspring brain development at birth. The brain is an energetically expensive tissue, both in terms of development and maintenance [69, 121, 122], and the brain is characterized by a unique lipid composition [123]. It is of no surprise that placentation strategies may affect nutrient availability for important developmental processes that vary among species. A more mechanistic understanding of how species-specific differences in nutrient transport affect these life history traits remains to be determined.

Non-esterified fatty acid (NEFA) availability for the conceptus can be from mobilization of maternal adipose depots or from local TG hydrolysis by maternal or placental lipases. The human placental microvillous membrane is capable of binding lipoproteins that transport triglyceride and other esterified lipids [124, 125] and the placenta has lipase activity to liberate NEFA from triglyceride [126, 127]. Indeed, studies from guinea pig indicate that more of the

NEFA available to placenta is derived from maternal TG than from circulating NEFA [128]. Increased lipase activity has been measured from placentae from diabetic pregnancies and the higher availability of maternal lipids may be associated with the increased fetal weight gain that is characteristic of gestational diabetes [126]. Placental lipases may have increased selectivity to release long-chain poly-unsaturated fatty acids from triglyceride because lipoprotein lipases preferentially hydrolyze the sn-2 position which is more likely to be unsaturated [37]. Different placental cell types may also contribute to making fatty acids available for uptake. For example, placental macrophages express high levels of lipoprotein lipase, and endothelial cell expression of endothelial lipase may contribute significantly to hydrolysis of maternal lipoproteins throughout gestation [129].

After fatty acids have been liberated from maternal TG at the microvillous membrane, they are available for placental transport and metabolism. Placental fatty acid binding proteins (FABPs) and fatty acid transport protein (FAT/CD36) may facilitate fatty acid transport down a concentration gradient [129]. In humans, the concentration of NEFA in maternal blood is about threefold higher than in fetal blood at term, but fetal blood has a higher concentration of albumin and a lower NEFA/albumin molar ratio than maternal blood [37, 130]. In this way, the fetus can exert a steeper effective concentration gradient to increase fetal fatty acid uptake which is particularly important during late gestation when fetal fat accretion is greatest in humans. The fatty acid transport proteins FATP1 (SLC27A1) and FATP4 (SLC27A4), two members of the very long-chain acyl-CoA synthetase family, are also expressed in placenta [129] and may help shuttle acyl groups to particular metabolic fates within the placenta [131–134]. Acyl-CoA thioesterases, which hydrolyze acyl-CoAs to free fatty acids and free coenzyme A in several cellular compartments, could conceivably play a role in making fatty acids available for transport as a free acid. One report has detected long-chain acyl-CoA thioesterase activity in BeWo human placental choriocarcinoma cells, and treatment of cells with particular fatty acids resulted in increased thioesterase activity and enhanced expression of PPARγ target genes [135]. Another way acyl groups could be transported across the placenta is as acylcarnitine species. Transacylation of long-chain acyl-CoAs to acylcarnitines is essential for long-chain fatty acid transport into the mitochondrial matrix for β-oxidation. The organic cation/carnitine transporter Octn2 is expressed in placenta [136], and carnitine levels in cord blood are higher than in maternal blood [137]. Blood acylcarnitine profiling of newborns is a common diagnostic approach to screen for metabolic deficiencies at birth [138].

It has been speculated that NEFA transported into placenta are likely esterified to placental TG, and fetal TG levels correlate with placental TG content (rather than with maternal circulating lipid concentrations) [117]. Placental TG is comprised of that which has been taken up from maternal lipoproteins (VLDL) and also from placental TG synthesis. Studies of rat placenta demonstrated that NEFA could be esterified in a concentration-dependent manner [139]. Placental TG content increased with progressing gestation, and a severe 48 h fast in rats also dramatically increased placental TG levels. Radiolabeled oleate was readily incorporated into TG, diacylglycerol, and cholesterol esters. There was no difference in the capacity for oleate esterification in placentae from fed vs fasted rat dams, suggesting that the capacity for esterification cannot account for the difference in TG content and that the availability of maternal circulating lipids may be a more important regulator of placental TG content [139]. A recent computational-experimental approach used human placental ex vivo perfusions to model fatty acid uptake and transfer to the fetus [140]. Placental uptake of fatty acids was largely dependent on placental metabolism of fatty acids rather than on microvillous membrane transport. The idea here is that when membrane transport capacity is high, the transmembrane gradient becomes small and the rate-determining factor becomes metabolism of the molecules of interest. Rates of fatty acid delivery to the fetal compartment were determined by placental metabolic pools and basal membrane transport [140]. In this way, placental lipid stores may accommodate on-going fetal lipid metabolic demand by making nutrients available independent of maternal dietary availability. Further studies are needed to characterize the metabolic fates of placental fatty acids to better understand how these pools of lipids affect transport and whether fatty acid β-oxidation provides energy for placental nutrient transport. The observation that the placenta may serve as a metabolic pool for fatty acid delivery to the fetus is in agreement with the observation that glucose transport is also best understood in terms of a three-pool model where maternal, placental, and fetal metabolism are all taken into consideration [141].

The capacity for and role of fatty acid oxidation in the placenta is not well understood. Human placenta was found to express the necessary enzymatic machinery for mitochondrial β-oxidation [142, 143]. Oleate oxidation by placental explants has been observed—although at lower rates than oleate esterification into neutral lipids—and was moderately increased with gestational age [139]. This study, however, cannot account for differences in fatty acid utilization among placental cell types, which may account for some of the differences in fatty acid oxidation vs esterification. To this end, isolated trophoblasts can oxidize fatty acids as a significant metabolic fuel, but the contribution of other cell types is less well understood [142]. Broadly, placental metabolism can affect nutrient availability by sequestering nutrients from the mother, by storing nutrients for subsequent delivery to the fetus, or by providing new or bio-transformed substrates

for fetal nutrition that were produced as a result of placental metabolism (in the case of fatty acids, the production and transport of acylcarnitines or ketone bodies as possible metabolites for transport) (Fig. 4). In this way, placental lipid metabolism can modify maternal–fetal metabolic communication.

Placental nutrient transport: essential nutrients

The transport and availability of metabolites that cannot be synthesized in the fetal compartment represents another important mode of maternal–fetal metabolic communication. The essential fatty acids [required for the synthesis of long-chain polyunsaturated fatty acids (PUFAs)] and the branched-chain amino acids (BCAAs: valine, leucine, and isoleucine) are included in this category and are required for biosynthetic processes. In a baboon model of maternal nutrient restriction, fetal plasma BCAAs were decreased and expression of placental amino acid transporters was also decreased [144]. Over the course of gestation, maternal plasma concentrations of BCAAs decrease, likely due to increased placental uptake [102]. Interestingly, the decrease in maternal plasma BCAAs occurs concomitantly with the increased peripheral insulin resistance that occurs during pregnancy, which is opposite of numerous studies linking elevated serum BCAAs and insulin resistance in the metabolic syndrome [145–148]. The uncoupling of elevated BCAAs and insulin resistance during pregnancy could be an important part of understanding the pathology of insulin resistance. Moreover, therapies to alter BCAA levels during pregnancy could be beneficial in gestational diabetes or fetal growth restriction. In a preliminary study, overweight pregnant women receiving micronutrient supplementation in early pregnancy had lower BCAA levels compared to control overweight pregnant women not receiving the supplement [149]. While birthweight outcomes or measures of maternal glucose homeostasis are not available from this trial, the study demonstrates the utility of nutritional supplementation to affect macronutrient uptake in ways that may promote healthy fetal growth and birth outcomes. Interestingly, feeding rodents a low-protein diet during gestation has been associated with lower maternal plasma PUFA levels and lower fetal brain PUFA content in phospholipids, suggesting that macronutrient crosstalk can alter nutrient availability [150].

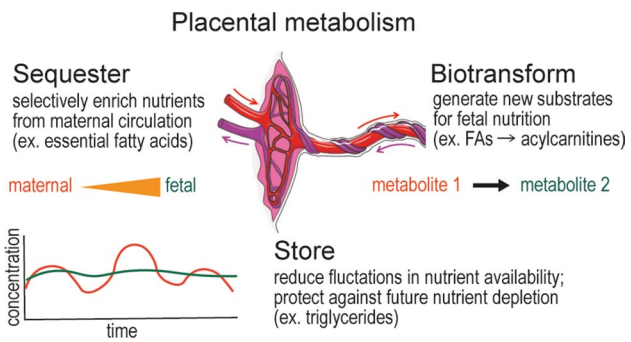

Fig. 4 Placental metabolism affects maternal–fetal metabolic communication. The placenta is not a passive conduit for nutrient and waste transfer. Placental metabolism can sequester nutrients from the mother, store nutrients for subsequent delivery to the fetus, or provide new or bio-transformed substrates for fetal nutrition. Examples are provided of lipids metabolized by the placenta in these ways. *Fas* fatty acids

There is no evidence for enrichment of essential fatty acids in maternal plasma across gestation. Despite large increases in the amount of circulating triglyceride, only slight increases in total circulating NEFA and phospholipids are observed across gestation with no robust changes in acyl composition in any lipid class [37, 102]. Long-chain polyunsaturated fatty acids (LCPUFAs) can be derived from the essential fatty acids linoleic acid (LA, 18:2 *n*-6) and α-linolenic acid (ALA, 18:3 *n*-3), but during pregnancy, LCPUFAs may become conditionally essential if dietary intake and biotransformation cannot keep pace with fetal demand [37]. Arachidonic acid (20:4 *n*-6), eicosapentaenoic acid (20:5 *n*-3), and docosahexaenoic acid (DHA) (22:6 *n*-3) are the metabolically most important LCPUFAs, and the very presence of these essential fatty acids in fetal tissues stands as evidence for fetal uptake and accumulation [37]. Intra-amniotic administration of isotopically labeled LA and ALA to fetal rats resulted in significant label incorporation into fetal liver and brain lipids, including in the form of DHA which implies fetal biosynthesis of PUFAs [151]. In the human fetus, lipid deposition increases exponentially with gestational age until it reaches the maximal rate of accretion of 7 g/day just before term [57], and DHA requirements triple from 100 to 300 mg/day from mid to late gestation [37]. One method of bioaccumulation of these lipids is the conversion of NEFA into phospholipids within the fetal liver to trap select fatty acids and accumulate them from the circulation [152]. Similarly, other tissues, most notably adipose, may serve as a pool for these lipids. While PUFAs are particularly important for mammalian brain development, remarkably, 16-fold more DHA is stored in fetal adipose tissue than is deposited in fetal brain, and this accumulation of DHA in adipose is specific to fetal adipose tissue and is not reflective of maternal adipose tissue DHA content [37].

The placenta also likely plays a major role in the selective uptake of PUFAs. Administration of ^{13}C-labeled fatty acids to pregnant women just prior to cesarean delivery revealed that placenta preferentially accumulated DHA relative to other labeled fatty acids (palmitate, oleate, and linoleate) at the concentrations tested [130]. Furthermore,

[^{13}C]DHA was esterified in similar proportions in cord blood NEFA, phospholipids, and triglyceride, while other tracers were primarily retained as NEFA or incorporated into TG [130]. These studies provide evidence for selective channeling of individual fatty acids into different placental pools and eventually into the fetal circulation. One way that DHA has been shown to cross membranes is via MFSD2a, the recently characterized lysophospholipid transporter that facilitates DHA accumulation in the developing brain [153, 154]. Without this transporter, mice exhibit microcephaly, impaired blood–brain barrier function, neuronal cell loss, and cognitive deficits [153, 154]. Placental expression of MFSD2a, the lysophosphatidylcholine-DHA transporter, was found to be decreased in women with gestational diabetes, and low levels of the DHA transporter were found to correlate with low levels of DHA in cord serum total lipids, although these levels still exceeded maternal circulating levels [155].

Placental elongation/desaturation of fatty acids is one way that fetal levels of LCPUFAs could be accumulated over maternal levels; however, there is little evidence of this activity in placenta [156]. Fetal and neonatal liver microsomes have the capacity to elongate and desaturate fatty acids [156, 157]. In addition, isotopic labeling studies in human infants administered labeled linoleic (18:2 *n*-6) and linolenic (18:3 *n*-3) acid resulted in labeled PUFAs in plasma fatty acids and phospholipids [152, 158]. Mice lacking *Elovl2*, a PUFA elongase, were used to characterize the maternal provision of and neonatal requirements for DHA [159]. These mice exhibit a systemic deficiency in DHA, including a 90% suppression in serum DHA concentrations that can be rescued by dietary DHA supplementation. Importantly, neonatal heterozygous mice reared by DHA-deficient null dams were able to compensate via neonatal synthesis of DHA, although the exact timing of when this capacity is established is not fully known [159]. Altogether, these examples demonstrate that there are multiple mechanisms in place to ensure adequate fetal uptake or neonatal synthesis of essential fatty acids required for mammalian brain development. Maternal, placental, and fetal adaptations work in concert to ensure adequate supply of essential nutrients.

Maternal–fetal metabolic communication in nutrient stress

Human pregnancy is characterized by greater metabolic flexibility than in the non-pregnant state to protect fetal growth from maternal nutrient deprivation [1]. The elevated levels of circulating lipid metabolites in fasting pregnant women combined with an earlier than normal shift from glucose to fat utilization by maternal tissues has been termed "accelerated starvation" [5, 160]. The acceleration is so dramatic that overnight fasting (14–18 h) in normal late term pregnancy leads to serum metabolite concentrations that rival the effects of 2–3 days of starvation in non-pregnant individuals [160, 161]. The features of the accelerated starvation response include increased fat mobilization from adipose, exaggerated ketone production, decreased blood glucose despite enhanced gluconeogenic capacity, and increased maternal muscle catabolism (reviewed in [5]) (Fig. 5a). Increased maternal utilization of lipids as metabolic fuel spares glucose and amino acids for fetal uptake [161]. Maternal hormones certainly play a role in these adaptations, but the accelerated fasting response is most apparent during late gestation when the conceptus is large enough to challenge maternal energy reserves. Fetal metabolic demand and fetal signals likely contribute to the maternal accelerated fasting response, especially during late gestation. Both lean and obese women (who gained similar amounts of weight from pre-conception) exhibited the hallmarks of the accelerated fasting response—reduced blood glucose and elevated free fatty acids and ketone bodies—on the same magnitude and timescale [161]. This finding is suggestive of fetoplacental signals directing the accelerated fasting response rather than maternal signals which may differ between lean and obese women. Late gestation is also characterized by "facilitated anabolism" which describes the aggregate changes in maternal circulating metabolites that promote fetal growth. The interaction between accelerated fasting and "facilitated anabolism" results in a pattern of dynamic metabolic oscillations in maternal fuel utilization between fed and fasted states during late term pregnancy—all to meet immediate maternal and fetal metabolic needs and to anticipate future nutrient depletion [5] (Fig. 5b).

Impaired fetal growth may be indicative of fetal metabolic deficiency, placental aberrations, maternal undernutrition, or impaired maternal nutrient partitioning. Nutrient deprivation during pregnancy has been studied in human populations experiencing famine [162, 163] or electing to fast during Ramadan [164–166]. Findings from these populations suggest that nutrient limitation may affect the nature and severity of maternal effects and postnatal outcomes differently during early vs late gestation. For instance, intermittent fasting during Ramadan reduced abdominal visceral fat thickness in pregnant women from 12 to 27 weeks gestation but was not associated with any discernable differences in fetal outcomes [165]. In another study, women who observed the Ramadan fast during the second or third trimester had significantly less maternal weight gain than others who did not fast [166]. Children born to mothers who fasted in the first trimester had lower birth weights than children born to mothers who fasted in the second or third trimesters [164]. Moreover, elevated cortisol levels were measured in women who fasted, and this could contribute to the maternal and

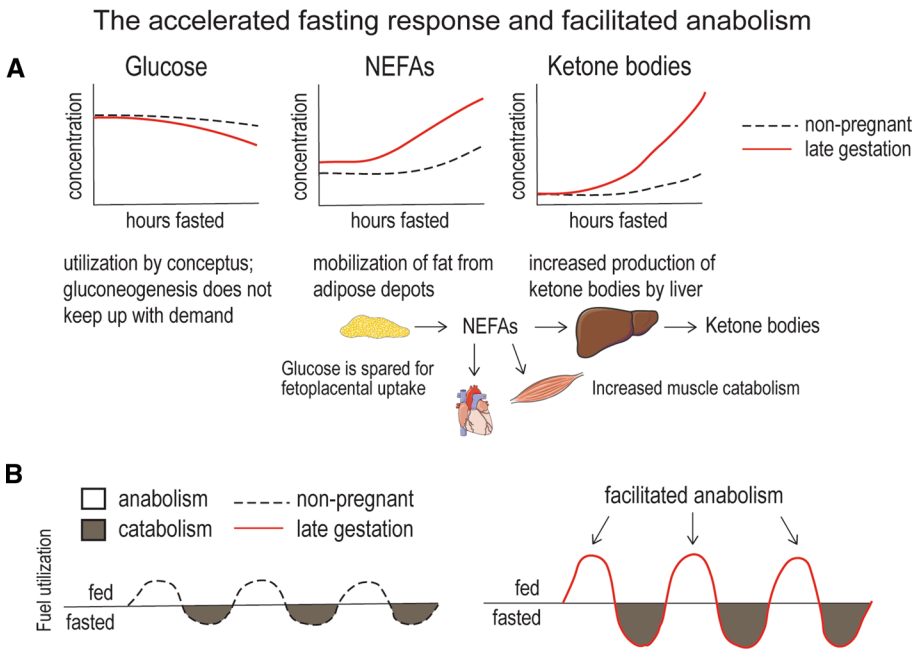

Fig. 5 The accelerated fasting response during pregnancy. **a** Fasting in normal late term pregnancy leads to robust increases in circulating lipids and exaggerated ketone body production [161], shown here as representative plasma concentrations in response to fasting during late gestation in red (black dashed line is non-pregnant control). Additional features of the accelerated fasting (or accelerated starvation) response include increased fat mobilization from adipose, decreased blood glucose despite enhanced gluconeogenic potential, and increased maternal muscle catabolism. Increased maternal utilization of lipids spares glucose and amino acids for fetal uptake. **b** Late gestation is also characterized by "facilitated anabolism" which describes aggregate changes in maternal circulating factors that promote fetal growth. Accelerated fasting and facilitated anabolism result in a pattern of dynamic metabolic oscillations in maternal fuel utilization between fed and fasted states in late gestation [5]. *NEFAs* non-esterified fatty acids

fetal differences in weight gain [167]. Related to this, placental expression of 11β-hydroxysteroid dehydrogenase, which normally serves to protect the fetus from maternal glucocorticoids, is down-regulated by maternal undernutrition, especially low-protein diets [168].

The nature of nutrient deprivation experienced by populations faced with food shortages and famine is entirely different from elective fasting. From patients who endured the Dutch famine of 1944–1945, prenatal famine exposure during early gestation led to slightly heavier and larger babies than controls not exposed to famine with increased rates of obesity and elevated risk of cardiovascular disease in adulthood [162]. Famine exposure during mid or late gestation was associated with lower birth weights and was correlated with impaired glucose tolerance in adulthood [162]. Low birth weight, especially when small for placental size, is strongly associated with the risk for cardiovascular disease later in life [81]. Early nutrient deprivation and the associated "catch-up" growth upon transitioning back to adequate nutrition may be particularly detrimental [169]. The Great Chinese Famine of 1959–1961 affected a larger population for a longer length of time than other widely studied food shortages of the twentieth century; as a result, studies of this population have the statistical power to reveal more subtle effects of nutritional deficiency. For example, women who were exposed to famine as fetuses have a higher risk of metabolic syndrome (obesity, hyperlipidemia, hypertension, and/or dysglycemia) than women who were exposed postnatally, and that risk is higher than for men regardless of whether they were exposed to famine prenatally or postnatally [170]. Another famine cohort from the Nigerian civil war (1967–1970) also associated fetal-infant exposure to famine with increased risk of hypertension and impaired glucose tolerance as adults [171]. The effects of fetal undernutrition among this sub-Saharan cohort were even more pronounced and emerged at earlier ages than European cohorts. The hypothesis of "early programming of disease" posits that many chronic adult diseases—including immune diseases, neuropsychiatric disorders, and other conditions that are not overtly "metabolic"—are in part determined by fetal and infant nutrition [1, 172]. The timing and duration of undernutrition during early development greatly affect chronic disease risk and manifestation. Animal models of intrauterine growth restriction in rats, rabbits, and sheep confirm that the timing and duration of maternal perturbations greatly affects fetal and neonatal outcomes [173–175]. Metabolites, hormones, and other secreted factors and adaptations to the presence of these signals likely play a role in

prenatal metabolic programming in ways that contribute to chronic adult diseases.

Fetoplacental response to nutrient stress

As the key interface for regulation of nutrient availability during pregnancy, how the placenta responds to maternal nutrient deprivation has the potential to greatly alter fetal outcomes. Ultimately, placental adaptations to the maternal environment will impact offspring physiology and postnatal health, as reviewed elsewhere [176]. The placental response could include structural or organizational changes that alter placental metabolism, hormonal communication, or transporter expression and activity. Chronic undernutrition during mouse pregnancy has been shown to result in these kinds of structural and functional adaptations in placental phenotype [177]. In the case of more acute nutrient deprivation, the timing of placental sensing and responding to maternal nutrient deprivation could occur before the fetus experiences nutrient limitation, at the same time as the fetus, or in response to fetal signals of metabolic demand not being met. The placental response to late-gestation fasting includes triglyceride accumulation, consistent with the elevation in maternal circulating lipid concentrations upon fasting [48, 139]. Studies in late-gestation pregnant rats demonstrated that placental incorporation of radiolabeled triglyceride preceded fetal incorporation of the radiolabeled lipid [117]. In addition, placental glycogen stores were decreased 40% by prolonged maternal fasting [178]. Select glycolytic, lipogenic, and gluconeogenic enzyme activities were measured in maternal liver, fetal liver, and placenta in fed or fasted rats. While maternal liver enzyme activities were dramatically altered by fasting, fetal liver enzyme activities were only modestly changed, and placental enzyme activities were unaffected [178]. Gestational age was found to be a better predictor of placental enzymatic activity than regulation by nutritional or hormonal influences, at least in the context of these in vitro assays that test the enzymatic capacity of a tissue.

During maternal starvation, or during an insulin-suppressed state such as streptozotocin-induced diabetes, fetal tissues were found to accumulate lipid in concert with elevated maternal serum triglyceride concentrations, which rose twofold in this rat model of diabetes during pregnancy [117]. A rabbit model of late-gestation maternal fasting demonstrated a similar dramatic increase in fetal lipid uptake and accumulation [29]. Moreover, the fetal capacity for lipid accumulation in rats increased over the course of gestation, tripling from day 17 to day 20 of gestation [117]. The accumulation of maternally derived lipids by the fetus may represent an adaptive mechanism to protect against further nutrient deprivation in utero and to prepare the fetus for the possibility of nutrient deficiency after parturition. Fatty acid oxidation by the fetal liver may provide energy for gluconeogenesis as it does in the adult fasting liver. The fetus can respond to maternal fasting, and the method of response may greatly alter neonatal outcomes when maternal–fetal metabolic communication is interrupted at parturition.

Maternal–fetal metabolic miscommunication

The previous examples demonstrate how maternal–fetal metabolic communication can dynamically respond to changing nutrient status, but it raises the question: What happens when metabolic communication is disrupted or metabolic/hormonal signals misinterpreted? Here, some metabolic disorders of pregnancy are described with particular attention to the miscommunication driving or resulting from these conditions.

Some pathologies of pregnancy develop as a result of a mismatch between fetal demands, maternal response, and maternal capacity to meet these needs. Gestational diabetes mellitus (GDM) is the most common metabolic abnormality during pregnancy, affecting 5–9% of pregnant women in the US [179]. Complications of GDM include increased birth weight (macrosomia) and predisposition of the mother to develop type 2 diabetes in the future [180]. Pregnancy has been described as a diabetogenic challenge where the increased glucose demand for fetal growth and development means changes in maternal metabolism to support and sustain this high glucose demand while maintaining maternal euglycemia [5]. In addition, GDM, like type 2 diabetes mellitus, has been described as a "disorder of total fuel metabolism" since all major classes of insulin-dependent substrates are affected: overnight fasted plasma glucose, NEFA, and TG are higher in patients with gestational diabetes than in unaffected pregnant women [5]. The combined increases of these nutrients likely contribute to the elevated risk of macrosomia in GDM pregnancies. Several adaptive responses to pregnancy contribute to the development of gestational diabetes, and many of these responses are likely mediated by hormonal (mis)communication. First, pregnancy is characterized by elevated insulin secretion and decreased peripheral insulin sensitivity. There was a 50–60% decrease in insulin-mediated glucose disposal in lean women from pregravid to late gestation [33, 181]. Pregnant women are tested for GDM with an oral glucose tolerance test at 24–28 weeks gestation, and a patient is diagnosed with GDM if her blood glucose is elevated after fasting or glucose challenge [180]. Elevated insulin concentrations are not part of the diagnostic criteria, but fasting plasma insulin of women with GDM during late gestation was 250% the levels of late-gestation weight-matched non-diabetic pregnant controls [182].

Women with GDM also demonstrated a twofold increase in fasting plasma insulin levels in late gestation relative to pre-gravid measurements [182]. A second adaptation of pregnancy that is dysregulated in GDM is the increase in gluconeogenic capacity. Isotopic labeling studies in pregnant women have demonstrated a 30% increase in total gluconeogenesis from early to late pregnancy (11–34 weeks gestation) [33]. Absolute rates of glucose infusion to maintain euglycemia were 22% lower in late-gestation GDM pregnancies relative to lean, weight-matched, and non-diabetic pregnant controls [181]. One explanation of GDM is that placental hormones that promote maternal liver gluconeogenesis outpace the ability of maternal insulin secretion (and sensitivity) to maintain euglycemia. Some studies have implicated placental growth hormone or placental lactogen as molecules which could contribute to the development and progression of GDM [4, 183]. Placental lactogen increases pancreatic beta cell proliferation during pregnancy, but it remains to be determined if the increase in insulin secretion is what induces insulin resistance during gestation [4]. Placental growth hormone may contribute to increased placental GLUT1 expression and fetal hyperglycemia. Diabetogenic contributions for prolactin, cortisol, and glucagon have also been described [184]. Patients with GDM may manage their condition with diet and physical activity or with insulin treatment if deemed necessary. Monogenic diabetes or "mature onset diabetes of the young" (MODY), although rare and representing only 1–2% of diabetes cases worldwide, presents some additional challenges during pregnancy. The treatment plan for pregnant diabetics may depend on maternal response to treatment, fetal genotype, and the placental transfer of certain classes of drugs (sulfonylureas). The treatment plan may change during gestation depending on fetal growth rates and maternal glycemic control [185]. Glycemic control is an important metabolic adaptation during pregnancy that, when dysregulated, may result in gestational diabetes.

Maternal liver is one of the main tissues regulating the metabolic effects of fasting during late gestation, including gluconeogenic potential and maternal lipid availability. Several liver disorders may present during the second half of gestation including preeclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP); intrahepatic cholestasis of pregnancy; and the rare but life-threatening acute fatty liver of pregnancy (AFLP) [186]. AFLP is characterized by liver failure and microvesicular steatosis, and there is a strong genetic connection to fetal fatty acid oxidation defects, most notably long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency [186]. *Lcad*$^{-/-}$ mice were born at lower than expected Mendelian ratios suggesting frequent gestational loss and an important role for fetal fatty acid oxidation [187]. Impaired fetal fatty acid degradation generates metabolic signals that also impair lipid handling by the mother. These complications of pregnancy demonstrate the intricate nature of maternal–fetal metabolic communication, particularly during late gestation when fetal energy demands are highest and the maternal energy economy may be most vulnerable. Nevertheless, clinical and nutritional interventions can help women with genetically diagnosed metabolic disorders have uneventful pregnancies and healthy babies [188–191].

Frontiers in defining maternal–fetal metabolic communication

Innovative investigations into maternal–fetal metabolic, hormonal, and immunological communication can define factors for gestational success in ways that inform interventions to promote healthy pregnancies. The use of genetic animal models and biochemical approaches to obtain a greater mechanistic understanding of maternal–fetal metabolic communication may improve treatments for common conditions such as gestational diabetes [179] as well as rare disorders with a genetic component [186]. In mouse models, baseline transcriptome analyses of maternal tissues across gestation provided insight into tissue-specific physiological adaptations of pregnancy that cannot be studied in women [192]. In addition, cross-fostering experiments in animal models can provide insight into metabolic adaptations during early postnatal life and how maternal contributions affect postnatal outcomes [193].

To study metabolites as mediators of maternal–fetal communication, advances in isotopic labeling approaches in vivo [91, 194, 195] and imaging technologies will advance the field [196–200]. Targeted and unbiased metabolomics analyses of maternal and fetal plasma may help in the identification of novel biomarkers and metabolites mediating maternal–fetal metabolic communication in health and disease (Table 1). In women undergoing caesarean delivery, the four-vessel method of sampling from the arteries and veins on either side of the placenta can provide a wealth of information about maternal and fetal metabolite gradients and placental function [201]. Advances in systems biology and longitudinal studies of human pregnancy across large populations with data about neonatal outcomes will also prove instrumental in future investigations into maternal–fetal metabolic communication. Large clinical trials such as the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [202–210] and the Pregnancy Outcome Prediction study [211] have provided a wealth of data about maternal and newborn metabolic health and birth outcomes. Proteomic characterization of maternal plasma has also enabled biomarker discovery with predictive power [212–214]. A longitudinal proteomics study of maternal plasma characterized 1125 proteins, of which 10% changed in abundance

Table 1 Metabolomic analyses of maternal and fetal circulating metabolites

Human					
Condition	Fluid or Tissue	Maternal/fetal	Analytical platform	Notes on study design or findings	References
Healthy pregnancy, 1st trimester	Plasma	Maternal (8–16 wk GA)	UHPLC-MS GC–MS	$n=50$ Pregnant women with 21 non-pregnant controls; 637 small molecules identified; 44% regulated by pregnancy (of which 81% lower in pregnancy); 14 metabolites changed as a function of GA	[240]
Healthy pregnancy, cross sectional	Plasma Urine	Maternal (11–40 wk GA)	NMR	$n=12$–30 Per trimester; correlations between plasma and urine metabolites	[241]
Healthy pregnancy, cross sectional	Plasma Amniotic fluid	Maternal (2nd and 3rd trimester and at delivery) Fetal (amniocentesis)	NMR	Plasma changes from 2nd to 3rd trimester in glycerol, ketone bodies, and choline; amniotic fluid changes in amino acids, carnitine, glucose, pyruvate	[242]
Healthy pregnancy, cross sectional and longitudinal	Serum	Maternal (13–30 wk GA)	NMR	Data from > 322 pregnancies; 80 metabolites, 7 circulating proteins, and 37 cytokines measured	[243]
Healthy pregnancy, longitudinal	Plasma	Maternal (13, 20, 30 wk GA)	UHPLC-MS FIA-MS	$n=167$; Measurements of amino acids, NEFAs, polar lipids, acylcarnitines in longitudinal study	[102]
Healthy pregnancy, intergenerational	Serum	Maternal (10–17 wk GA) Fetal (umbilical venous cord blood) Child (10 years old)	UHPLC-MS FIA-MS	994 mother–child pairs; low correlation between samples from pregnancy, birth, and childhood but reference for future intergenerational metabolomic studies	[244]
Healthy pregnancy vs gestational diabetes mellitus (GDM), longitudinal	Serum	Maternal (13 and 26 wk GA)	UHPLC-MS	$n=107$ GDM patients and 107 matched controls; longitudinal changes in amino acids and phospholipids differ between GDM and controls	[245]
Healthy pregnancy vs poor perinatal outcome	Serum	Maternal (3rd trimester)	UHPLC-MS	$n=40$ small for gestational age, preterm birth, NICU admission; 98 metabolic features including lipids and steroid hormones	[246]
Healthy pregnancy, cross sectional, type of delivery	Placenta	Placenta	GC–MS UHPLC-MS	$n=5$–11; samples from pregnancies with preeclampsia also analyzed; changes in lipid species across gestation	[247]
Fetal central nervous system anomalies (CNSA)	Serum	Maternal (2nd trimester)	GC–MS	$n=70$ cases and 98 controls; increased short-chain organic acids and decreased fatty acids associated with CNSA	[248]

Table 1 (continued)

Human					
Fetal growth restriction (FGR)	Serum	Fetal (cord blood/umbilical vein)	LC–MS	$n=21$–22; elevated essential amino acids phenylalanine, tryptophan, and methionine in FGR	[249]
Fetal growth restriction (FGR) and preterm birth	Plasma	Maternal Fetal (umbilical venous and umbilical arterial)	LC–MS	Increased medium- and short-chain acylcarnitines in fetal plasma from very low birthweight cohort; changes in maternal–fetal polyamine concentrations	[250]
Fetal growth restriction (FGR)	Plasma	Maternal Fetal (cord blood/umbilical vein)	NMR	$n=25$–28; maternal and cord blood samples with lipid profiles	[251]
Fetal growth restriction (FGR), longitudinal sampling	Serum	Maternal (12, 20, 28 wk GA)	UHPLC-MS	$n=175$ cases and 299 controls; ratios of two positively and two negatively associated metabolites predicted FGR at term	[211]
Gestational diabetes mellitus (GDM)	Review of metabolomic profiling studies of women with GDM and their offspring				[252]
Gestational diabetes mellitus (GDM)	Serum	Maternal (1st trimester)	LC–MS	Diagnosed with GDM in 3rd trimester, $n=96$, matched for age, BMI, gravidity, parity; no significant difference in BCAAs	[253]
Gestational diabetes mellitus (GDM)	Serum	Maternal (12–16 wk GA)	NMR Lipid panel	82 GDM patients from a prospective study of 357 overweight and obese women; elevated isoleucine and leucine in GDM; specific lipoprotein profile in GDM	[254]
Gestational diabetes mellitus (GDM)	Serum	Maternal (3rd trimester and postpartum)	UHPLC-MS (QTOF)	$n=10$–12; candidate biomarkers in carbohydrate, amino acid, and lipid metabolism	[255]
Gestational diabetes mellitus (GDM)	Serum	Maternal (15–19 wk GA and 23–30 wk GA)	NMR Lipid panel	646 obese women (198 with GDM); higher BCAAs and different lipid profile in women diagnosed with GDM	[256]
Gestational diabetes mellitus (GDM) treated with insulin, metformin, or diet change only	Serum	Maternal (30 and 36 wk GA)	NMR	$n=107$–126; changes in amino acid profiles with different treatments	[257]
Gestational diabetes mellitus (GDM)	Serum	Fetal (cord blood) Maternal	HPLC–MS Flow injection electrospray ionization MS (FIA-ESI–MS)	412 mother–child pairs ($n=31$ with GDM); 54 metabolites in cord blood associated with GDM	[258]
Gestational diabetes mellitus (GDM)	Serum	Fetal (umbilical artery cord blood) Maternal	GC-FID (flame ionization detection)	174 mother–child pairs (84 with GDM); changes observed in fatty acid (PUFA) concentrations	[259]

Table 1 (continued)

Human					
Maternal oral glucose tolerance test (oGTT) and maternal hyperglycemia	Serum	Maternal (24–32 wk GA)	GC–MS	Fasting and 1 h post-oGTT serum samples ($n=400$); metabolites associated with maternal fasting hyperglycemia and newborn outcomes	[205]
Maternal oral glucose tolerance test (oGTT) GDM	Serum	Maternal	LC–MS	Before and 2 h after oGTT at 24–28wk GA; oGTT resulted in decreased acylcarnitines, fatty acids, and diacylglycerols; features significantly associated with GDM identified (23 GDM diagnoses/100 women)	[260]
Maternal hyperglycemia and GDM	Serum	Maternal (24–32 wk GA)	GC–MS LC–MS	Fasting and 1 h post-oGTT serum samples ($n=400$); results stratified by BMI and by 4 ancestry groups	[206]
Maternal hyperglycemia	Serum	Maternal (24–32 wk GA)	GC–MS LC–MS	$n=50$ and 67 with normal and high fasting plasma glucose; correlations with birth outcomes	[204]
Maternal hyperglycemia	Plasma Serum	Fetal (cord blood) Maternal (24–32 wk GA)	GC–MS LC–MS	$n=400\times4$ ancestry groups; cord plasma and maternal fasting serum; stratified by maternal BMI and glycemia	[207]
Maternal hyperglycemia and newborn adiposity	Serum	Maternal (24–32 wk GA)	GC–MS	$n=400\times4$ ancestry groups; maternal fasting and 1 h post-oGTT serum; correlations with newborn adiposity	[209]
Maternal hyperglycemia and newborn adiposity	Plasma	Fetal (cord blood)	GC–MS	$n=400\times4$ ancestry groups; correlations with newborn adiposity; BCAAs, NEFA, and TG positively associated with birthweight	[210]
Newborn adiposity	Plasma	Maternal (12, 20, 30 wk GA)	UHPLC-MS FIA-MS	Longitudinal plasma samples from 253 mothers; PUFAs in several phosphatidylcholine species negatively associated with neonatal adiposity	[261]
Maternal diet	Amniotic fluid Serum, urine	Fetal (2nd trimester amniocentesis) Maternal	NMR	$n=32$–33; hierarchical clustering of self-reported dietary patterns; maternal urine and serum samples	[262]
Maternal supraphysiological hypercholesterolemia (MSPHC)	Serum	Maternal Fetal (umbilical vein and artery)	UHPLC-MS (QTOF) Lipidomics	414 women, $n=30$ each MSPHC or MPHC; associations with maternal 1st trimester lipid panel	[263]
Preeclampsia (PE)	Serum Urine	Maternal	NMR	Matched for GA 35 wk [264]; Prospective study of 599 women (21 developed PE), GA 11–14 wk [265]	[264, 265]

Table 1 (continued)

Human					
Preeclampsia (PE)	Serum	Maternal (8–14 wk GA)	UHPLC-MS	Early-onset ($n=68$) and late-onset ($n=99$) cases; stearoylcarnitine as a potential biomarker	[266]
Preeclampsia (PE)	Serum	Maternal	NMR	Late-onset PE; elevated BCAAs in late PE	[267]
Preeclampsia (PE)	Serum	Maternal (26–41 wk GA)	NMR	PE and PE + FGR and small-for-GA and preterm cohorts; defined metabolites predictive for PE, less robust for FGR	[268]
Preeclampsia (PE)	Placenta	Placenta	NMR	$n=15$–19; severe PE and PE + FGR groups; correlations to serum biomarkers	[269]
Recurrent spontaneous abortion	Plasma	Maternal	GC–MS LC–MS	$n=50$, matched for age, GA, and BMI; amino acid metabolites as potential biomarkers	[270]
Non-human primate models					
Maternal nutrient restriction	Plasma Liver	Fetal Mid—(0.5) and late (0.9) gestation (*Papio hamadryas anubis*)	LC–MS	Maternal nutrient restriction (NR) to 70% of control pregnant baboons' consumption; fetal plasma short-chain acylcarnitines elevated in NR mid-gestation; certain amino acids reduced in NR late-gestation	[271]
Maternal western diet or diet reversal	Serum Liver	Fetal (umbilical artery) (*Macaca fuscata*)	UHPLC-MS	Features normalized by diet reversal or not normalized; correlations with hepatic TG	[98]
Longitudinal, developmental	Plasma	Fetal, Neonatal (*Macaca nemestrina*)	GC × GC-TOFMS	Umbilical arterial catheter at delivery and subsequent blood collections at 5 min, 1, 3, 6, 12, 24, 48, and 72 h after birth	[272]
Other animal models					
Chronic maternal cortisol excess (Sheep)	Serum	Fetal (late gestation) Maternal	NMR	Alterations in fetal serum amino acids and TCA cycle intermediates (no change in maternal serum)	[273]
Fetal growth restriction (FGR) (Pig)	Plasma	Fetal (90 or 110 days GA) (umbilical vein) Maternal	HPLC–MS (QTOF)	Changes observed in plasma amino acids at both gestational ages in FGR fetal pigs	[274]
Dietary model (High-fat diet) (Mouse)	Plasma	Maternal (6.5 days GA)	GC–MS LC–MS	High-fat diet (HFD) increased fatty acids and sphingolipids in early gestation maternal plasma; HFD alters early placenta transcriptome and impairs late-gestation placental microvessel density	[275]

Table 1 (continued)

Human					
Genetic model (Mouse)	Plasma	Fetal (19.5 days GA)	CE-TOFMS	Loss-of-function of Slc38a4/SNAT4, an amino acid transporter at the plasma membrane, results in placental hypoplasia; lower amino acid concentrations in Slc38a4 null fetal plasma	[276]
Genetic model (Mouse)	Plasma Placenta	Fetal (18.5 days GA) Maternal (18.5 days GA)	CE-TOFMS	Metabolomic analysis of wild-type and ezrin knockout mice implicated defect in hypotaurine transport in ezrin knockout mice	[277]
Genetic model (Mouse)	Serum	Maternal (18.5 days GA)	LC–MS FIA-MS	Mouse models of PE and FGR: control, $COMT^{-/-}$, and $Nos3^{-/-}$ pregnant mice (± a treatment that rescues fetal growth in $COMT^{-/-}$ mice)	[278]
Genetic model (Mouse)	Serum	Maternal (17.5 days GA)	NMR LC–MS	Genetic deficiency in mitochondrial pyruvate or fatty acid metabolism; maternal serum and non-pregnant controls; maternal blood and fetal liver acylcarnitines	[48]
Environmental cold stress (Rat)	Serum	Maternal (21 days GA)	LC–MS	3- or 7-day cold stress (4 °C) during late gestation; changes in lipid and amino acid metabolites	[279]
Effects of maternal gut microbiota (Mouse)	Plasma	Maternal Fetal (18.5 days GA)	UHPLC-MS GC–MS	Maternal and fetal plasma on high- and low-fiber diets; plasma metabolomics of specific-pathogen-free and germ-free mice	[280]

Ref. reference, *FGR* fetal growth restriction, *CNSA* central nervous system anomalies, *GDM* gestational diabetes mellitus, *BMI* body mass index, *GA* gestational age, *wk* weeks, *PUFA* polyunsaturated fatty acids, *oGTT* oral glucose tolerance test, *NICU* neonatal intensive care unit, *MSPHC* maternal (supra)physiological hypercholesterolemia, *min* minutes, *h* hours, *LC* liquid chromatography, *MS* mass spectrometry, *NMR* ^{1}H nuclear magnetic resonance spectroscopy, *UHPLC* ultra-high-performance liquid chromatography, *FIA* flow injection analysis, *GC* gas chromatography, *QTOF* quadropole time-of-flight, *TOF* time-of-flight, *CE* capillary electrophoresis

with gestational age, and nine proteins increased more than fivefold from 8 to 37 weeks [215]. Expanding these longitudinal studies to include patients with pregnancy complications has the potential to inform new diagnostic markers and therapeutic targets. Together, systems biology approaches to maternal–fetal health may inform mechanistic research and may enable personalized clinical interventions for pregnant women [216].

A relatively new and growing field of investigation in maternal–fetal communication includes the study of exosomes, which are membrane-bound extracellular vesicles that contain cytoplasmic components of the cells from which they were released [217–219]. Trophoblasts secrete exosomes containing placenta-specific microRNAs into the maternal circulation [220], and a select class of trophoblast microRNAs can be detected in maternal blood as early as 2 weeks after implantation [221]. Placental exosomes may play an important role in placental development and syncytiotrophoblast fusion [222], and exosomes derived from maternal adipose tissue could mediate cross-tissue communication between the placenta and maternal tissues [223]. Experimental delivery of exosomes will guide hypothesis-driven research in exosome biology during gestation [224, 225]. Exosomes may also be a way of delivering placental cargo to the fetus; exosomes from umbilical cord mesenchymal stem cells have been detected in umbilical blood [226], and a recent study has characterized exosomes containing a class of placenta-enriched microRNAs in human fetal plasma (umbilical cord venous blood) [227]. Postnatally, milk exosomes may contribute to neonatal nutrition and immunity [228]. Altogether, exosomes and their cargo may provide an additional means of communication between mother and offspring.

In addition to cell-derived extracellular vesicles, circulating cells may also be a means of maternal–fetal communication. Longitudinal transcriptomic and proteomic studies of immune cell changes during pregnancy have defined key immunological events [229, 230]. Single circulating trophoblast testing could be a valuable prenatal diagnostic tool [231]. In addition, sequencing cell-free circulating DNA or RNA could become important clinical platforms to screen for fetal genetic anomalies, to assess placental development, or to determine gestational age [232–234]. The presence of fetal or placental cells in the maternal circulation suggests that there could be biological consequences related to the presence of these cells. Indeed, fetal cells can repair injured maternal heart, and placenta-derived cells can be administered to non-pregnant mice to promote cardiovascular repair in the context of myocardial injury [235, 236]. The bidirectional exchange of maternal and fetal cells that persist unrejected in tissues postnatally results in microchimerism [237–239]. The presence of fetal cells in tissues that participate in maternal resource allocation, for instance, could alter nutrient partitioning and could affect intergenerational cooperation and conflict, to put it in terms of evolutionary biology [238]. Microchimerism may also contribute to health and disease in later life, and the effects of microchimerism on autoimmune disease and cancer are under investigation [237, 238]. The expanded immune tolerance from exposure to fetal microchimeric cells can also promote reproductive fitness by improving the outcomes of future pregnancies [239]. In this way, circulating maternal and fetal cells and the presence of genetically foreign cells in maternal and offspring tissues can contribute to maternal–fetal communication about nutrient partitioning and metabolism.

Conclusions

Maternal–fetal metabolic communication is dynamic to meet fetal metabolic demand upon changes in maternal nutrient status. This review has broadly summarized fetal macronutrient need and maternal metabolic adaptations during gestation. The types of signals that participate in maternal–fetal dialogue have been described, and future studies of these factors will begin to address the following questions: What is the fetal response to maternal nutrient deprivation or overnutrition? How is the metabolic state sensed, and which metabolites, endocrine molecules, and other signals contribute to metabolic communication between mother and fetus? And what is the role of the placenta in both sensing and adapting to this affront to fetal metabolism? A greater understanding of maternal–fetal metabolic communication in health and disease can inform diagnostic biomarkers for metabolic disorders of pregnancy as well as personalized clinical and nutritional interventions to promote healthy pregnancies, healthy offspring, and healthy populations.

Acknowledgements This work was supported by the US National Institutes of Health NHLBI T32-HL007843-23 (CEB) and R01DK116746 (MJW).

Author contribution Conceptualization: CEB and MJW; literature search and drafting: CEB; critical revision and editing: all the authors.

References

1. Prentice AM, Goldberg GR (2000) Energy adaptations in human pregnancy: limits and long-term consequences. Am J Clin Nutr 71(5 Suppl):1226S-1232S
2. Barker DJ (1990) The fetal and infant origins of adult disease. BMJ (Clin Res Ed) 301(6761):1111
3. Blackburn ST (2007) Maternal, fetal, and neonatal physiology: a clinical perspective, 3rd edn. Saunders, Philadelphia
4. Yamashita H, Shao J, Friedman JE (2000) Physiologic and molecular alterations in carbohydrate metabolism during pregnancy and gestational diabetes mellitus. Clin Obstet Gynecol 43(1):87–98

5. Freinkel N (1980) Banting lecture 1980. Of pregnancy and progeny. Diabetes 29(12):1023–1035
6. Butte NF, Wong WW, Treuth MS, Ellis KJ, O'Brian Smith E (2004) Energy requirements during pregnancy based on total energy expenditure and energy deposition. Am J Clin Nutr 79(6):1078–1087
7. Kopp-Hoolihan LE, van Loan MD, Wong WW, King JC (1999) Longitudinal assessment of energy balance in well-nourished, pregnant women. Am J Clin Nutr 69(4):697–704
8. Dewar AD (1953) Total metabolism of the mouse after pseudoparturition and parturition. Q J Exp Physiol Cogn Med Sci 38(4):263–294
9. Haig D (1993) Genetic conflicts in human pregnancy. Q Rev Biol 68(4):495–532
10. Haig D (1996) Altercation of generations: genetic conflicts of pregnancy. Am J Reprod Immunol 35(3):226–232
11. Fowden AL, Coan PM, Angiolini E, Burton GJ, Constancia M (2011) Imprinted genes and the epigenetic regulation of placental phenotype. Prog Biophys Mol Biol 106(1):281–288. https://doi.org/10.1016/j.pbiomolbio.2010.11.005
12. Tunster SJ, Jensen AB, John RM (2013) Imprinted genes in mouse placental development and the regulation of fetal energy stores. Reproduction (Cambridge, England) 145(5):R117-137. https://doi.org/10.1530/rep-12-0511
13. Varmuza S, Miri K (2015) What does genetics tell us about imprinting and the placenta connection? Cell Mol Life Sci 72(1):51–72. https://doi.org/10.1007/s00018-014-1714-0
14. Cassidy FC, Charalambous M (2018) Genomic imprinting, growth and maternal–fetal interactions. J Exp Biol. https://doi.org/10.1242/jeb.164517
15. de Waal E, Vrooman LA, Fischer E, Ord T, Mainigi MA, Coutifaris C, Schultz RM, Bartolomei MS (2015) The cumulative effect of assisted reproduction procedures on placental development and epigenetic perturbations in a mouse model. Hum Mol Genet 24(24):6975–6985. https://doi.org/10.1093/hmg/ddv400
16. Rhon-Calderon EA, Vrooman LA, Riesche L, Bartolomei MS (2019) The effects of assisted reproductive technologies on genomic imprinting in the placenta. Placenta 84:37–43. https://doi.org/10.1016/j.placenta.2019.02.013
17. Moore T, Haig D (1991) Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet 7(2):45–49. https://doi.org/10.1016/0168-9525(91)90230-n
18. Creeth HDJ, McNamara GI, Tunster SJ, Boque-Sastre R, Allen B, Sumption L, Eddy JB, Isles AR, John RM (2018) Maternal care boosted by paternal imprinting in mammals. PLoS Biol 16(7):e2006599. https://doi.org/10.1371/journal.pbio.2006599
19. Napso T, Yong HEJ, Lopez-Tello J, Sferruzzi-Perri AN (2018) The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation. Front Physiol 9:1091. https://doi.org/10.3389/fphys.2018.01091
20. Silva JF, Serakides R (2016) Intrauterine trophoblast migration: a comparative view of humans and rodents. Cell Adhesion Migr 10(1–2):88–110. https://doi.org/10.1080/19336918.2015.1120397
21. Coan PM, Ferguson-Smith AC, Burton GJ (2004) Developmental dynamics of the definitive mouse placenta assessed by stereology. Biol Reprod 70(6):1806–1813. https://doi.org/10.1095/biolreprod.103.024166
22. Elliot MG, Crespi BJ (2008) Placental invasiveness and brain-body allometry in eutherian mammals. J Evol Biol 21(6):1763–1778. https://doi.org/10.1111/j.1420-9101.2008.01590.x
23. Grosser O (1909) Vergleichende Anatomie und Entwicklungsgeschichte der Eihaute und der Placenta. Wilhelm Braumuller, Vienna
24. Rossant J, Cross JC (2001) Placental development: lessons from mouse mutants. Nat Rev Genet 2(7):538–548. https://doi.org/10.1038/35080570
25. Dilworth MR, Sibley CP (2013) Review: transport across the placenta of mice and women. Placenta 34(Suppl):S34-39. https://doi.org/10.1016/j.placenta.2012.10.011
26. Sandovici I, Hoelle K, Angiolini E, Constancia M (2012) Placental adaptations to the maternal–fetal environment: implications for fetal growth and developmental programming. Reprod Biomed Online 25(1):68–89. https://doi.org/10.1016/j.rbmo.2012.03.017
27. Grigsby PL (2016) Animal models to study placental development and function throughout normal and dysfunctional human pregnancy. Semin Reprod Med 34(1):11–16. https://doi.org/10.1055/s-0035-1570031
28. Duyne CMV, Parker HR, Havel RJ, Holm LW (1960) Free fatty acid metabolism in fetal and newborn sheep. Am J Physiol Legacy Content 199(6):987–990. https://doi.org/10.1152/ajplegacy.1960.199.6.987
29. Edson JL, Hudson DG, Hull D (1975) Evidence of increased fatty acid transfer across the placenta during a maternal fast in rabbits. Biol Neonate 27(1–2):50–55. https://doi.org/10.1159/000240758
30. Abbot P, Rokas A (2017) Mammalian pregnancy. Curr Biol 27(4):R127-r128. https://doi.org/10.1016/j.cub.2016.10.046
31. Guernsey MW, Chuong EB, Cornelis G, Renfree MB, Baker JC (2017) Molecular conservation of marsupial and eutherian placentation and lactation. eLife. https://doi.org/10.7554/eLife.27450
32. Battaglia FC, Meschia G (1978) Principal substrates of fetal metabolism. Physiol Rev 58(2):499–527
33. Kalhan S, Rossi K, Gruca L, Burkett E, O'Brien A (1997) Glucose turnover and gluconeogenesis in human pregnancy. J Clin Invest 100(7):1775–1781
34. Longo LD (1983) Maternal blood volume and cardiac output during pregnancy: a hypothesis of endocrinologic control. Am J Physiol 245(5 Pt 1):R720-729
35. Osol G, Cipolla M (1993) Pregnancy-induced changes in the three-dimensional mechanical properties of pressurized rat uteroplacental (radial) arteries. Am J Obstet Gynecol 168(1 Pt 1):268–274. https://doi.org/10.1016/s0002-9378(12)90924-2
36. Cipolla M, Osol G (1994) Hypertrophic and hyperplastic effects of pregnancy on the rat uterine arterial wall. Am J Obstet Gynecol 171(3):805–811. https://doi.org/10.1016/0002-9378(94)90102-3
37. Haggarty P (2010) Fatty acid supply to the human fetus. Annu Rev Nutr 30:237–255. https://doi.org/10.1146/annurev.nutr.012809.104742
38. Rennie MY, Whiteley KJ, Adamson SL, Sled JG (2016) Quantification of gestational changes in the uteroplacental vascular tree reveals vessel specific hemodynamic roles during pregnancy in mice. Biol Reprod 95(2):43. https://doi.org/10.1095/biolreprod.116.140681
39. Avni R, Raz T, Biton IE, Kalchenko V, Garbow JR, Neeman M (2012) Unique in utero identification of fetuses in multifetal mouse pregnancies by placental bidirectional arterial spin labeling MRI. Magn Reson Med 68(2):560–570. https://doi.org/10.1002/mrm.23246
40. Raz T, Avni R, Addadi Y, Cohen Y, Jaffa AJ, Hemmings B, Garbow JR, Neeman M (2012) The hemodynamic basis for positional- and inter-fetal dependent effects in dual arterial supply of mouse pregnancies. PLoS ONE 7(12):e52273. https://doi.org/10.1371/journal.pone.0052273
41. Even MD, Laughlin MH, Krause GF, vom Saal FS (1994) Differences in blood flow to uterine segments and placentae in relation to sex, intrauterine location and side in pregnant rats. J Reprod Fertil 102(1):245–252

42. Coe BL, Kirkpatrick JR, Taylor JA, vom Saal FS (2008) A new "crowded uterine horn" mouse model for examining the relationship between foetal growth and adult obesity. Basic Clin Pharmacol Toxicol 102(2):162–167. https://doi.org/10.1111/j.1742-7843.2007.00195.x
43. Knopp RH, Herrera E, Freinkel N (1970) Carbohydrate metabolism in pregnancy. 8. Metabolism of adipose tissue isolated from fed and fasted pregnant rats during late gestation. J Clin Investig 49(7):1438–1446. https://doi.org/10.1172/JCI106361
44. Elliott JA (1975) The effect of pregnancy on the control of lipolysis in fat cells isolated from human adipose tissue. Eur J Clin Invest 5(2):159–163
45. Herrera E, Amusquivar E, Lopez-Soldado I, Ortega H (2006) Maternal lipid metabolism and placental lipid transfer. Horm Res 65(Suppl 3):59–64. https://doi.org/10.1159/000091507
46. Hytten FE (1981) Weight gain in pregnancy—30 year of research. S Afr Med J 60(1):15–19
47. Argiles J, Herrera E (1981) Lipids and lipoproteins in maternal and fetus plasma in the rat. Biol Neonate 39(1–2):37–44. https://doi.org/10.1159/000241390
48. Bowman CE, Selen Alpergin ES, Cavagnini K, Smith DM, Scafidi S, Wolfgang MJ (2019) Maternal lipid metabolism directs fetal liver programming following nutrient stress. Cell Rep 29(5):1299–1310. https://doi.org/10.1016/j.celrep.2019.09.053
49. Zhang L, Sugiyama T, Murabayashi N, Umekawa T, Ma N, Kamimoto Y, Ogawa Y, Sagawa N (2011) The inflammatory changes of adipose tissue in late pregnant mice. J Mol Endocrinol 47(2):157–165. https://doi.org/10.1530/jme-11-0030
50. Jones CT (1976) Lipid metabolism and mobilization in the guinea pig during pregnancy. Biochem J 156(2):357–365. https://doi.org/10.1042/bj1560357
51. Vernon RG, Clegg RA, Flint DJ (1981) Metabolism of sheep adipose tissue during pregnancy and lactation. Adaptation and regulation. Biochem J 200(2):307–314. https://doi.org/10.1042/bj2000307
52. Chassen SS, Ferchaud-Roucher V, Palmer C, Li C, Jansson T, Nathanielsz PW, Powell TL (2020) Placental fatty acid transport across late gestation in a baboon model of intrauterine growth restriction. J Physiol 598(12):2469–2489. https://doi.org/10.1113/JP279398
53. Zilversmit DB, Hughes LB, Remington M (1972) Hypolipidemic effect of pregnancy in the rabbit. J Lipid Res 13(6):750–756
54. Mizoguchi Y, Matsuoka T, Mizuguchi H, Endoh T, Kamata R, Fukuda K, Ishikawa T, Asano Y (2010) Changes in blood parameters in New Zealand White rabbits during pregnancy. Lab Anim 44(1):33–39. https://doi.org/10.1258/la.2009.008002
55. Piccione G, Caola G, Giannetto C, Grasso F, Calanni Runzo S, Zumbo A, Pennisi P (2009) Selected biochemical serum parameters in ewes during pregnancy, post-parturition, lactation and dry period. Anim Sci Pap Rep 27(4):321–330
56. Girard J, Ferre P, Pegorier JP, Duee PH (1992) Adaptations of glucose and fatty acid metabolism during perinatal period and suckling-weaning transition. Physiol Rev 72(2):507–562
57. Widdowson EM (1968) Growth and composition of the fetus and newborn. In: Assali NS (ed) The biology of gestation, 2nd edn. Academic, New York, pp 1–49
58. Morrison SD (1956) The total energy and water metabolism during pregnancy in the rat. J Physiol 134(3):650–664
59. Valcarce C, Cuezva JM, Medina JM (1985) Increased gluconeogenesis in the rat at term gestation. Life Sci 37(6):553–560. https://doi.org/10.1016/0024-3205(85)90468-0
60. Richard D, Trayhurn P (1985) Energetic efficiency during pregnancy in mice fed ad libitum or pair-fed to the normal energy intake of unmated animals. J Nutr 115(5):593–600
61. Cunnane SC, Crawford MA (2003) Survival of the fattest: fat babies were the key to evolution of the large human brain. Comp Biochem Physiol A Mol Integr Physiol 136(1):17–26. https://doi.org/10.1016/s1095-6433(03)00048-5
62. Nagy LE, King JC (1984) Postprandial energy expenditure and respiratory quotient during early and late pregnancy. Am J Clin Nutr 40(6):1258–1263
63. Forsum E, Lof M (2007) Energy metabolism during human pregnancy. Annu Rev Nutr 27:277–292. https://doi.org/10.1146/annurev.nutr.27.061406.093543
64. Catalano PM, Roman-Drago NM, Amini SB, Sims EA (1998) Longitudinal changes in body composition and energy balance in lean women with normal and abnormal glucose tolerance during pregnancy. Am J Obstet Gynecol 179(1):156–165
65. Butte NF, Hopkinson JM, Mehta N, Moon JK, Smith EO (1999) Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. Am J Clin Nutr 69(2):299–307
66. Qiao L, Lee S, Nguyen A, Hay WW Jr, Shao J (2018) The regulatory effects of brown adipose tissue thermogenesis on maternal metabolic adaptation, placental efficiency, and fetal growth in mice. Am J Physiol Endocrinol Metab. https://doi.org/10.1152/ajpendo.00192.2018
67. Lopaschuk GD, Spafford MA, Marsh DR (1991) Glycolysis is predominant source of myocardial ATP production immediately after birth. Am J Physiol Heart Circ Physiol 261(6):H1698–H1705
68. Fisher DJ, Heymann MA, Rudolph AM (1981) Myocardial consumption of oxygen and carbohydrates in newborn sheep. Pediatr Res 15(5):843–846
69. Cremer JE (1982) Substrate utilization and brain development. J Cereb Blood Flow Metab 2(4):394–407. https://doi.org/10.1038/jcbfm.1982.45
70. Arizmendi C, Medina JM (1983) Lactate as an oxidizable substrate for rat brain in vitro during the perinatal period. Biochem J 214(2):633–635
71. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, Yang C, Do QN, Doucette S, Burguete D, Li H, Huet G, Yuan Q, Wigal T, Butt Y, Ni M, Torrealba J, Oliver D, Lenkinski RE, Malloy CR, Wachsmann JW, Young JD, Kernstine K, DeBerardinis RJ (2017) Lactate metabolism in human lung tumors. Cell 171(2):358-371.e359. https://doi.org/10.1016/j.cell.2017.09.019
72. Hui S, Ghergurovich JM, Morscher RJ, Jang C, Teng X, Lu W, Esparza LA, Reya T, Le Z, Yanxiang Guo J, White E, Rabinowitz JD (2017) Glucose feeds the TCA cycle via circulating lactate. Nature 551(7678):115–118. https://doi.org/10.1038/nature24057
73. Baker C, Ebert S (2013) Development of aerobic metabolism in utero: Requirement for mitochondrial function during embryonic and fetal periods. OA Biotechnol. https://doi.org/10.13172/2052-0069-2-2-571
74. Johnson MT, Mahmood S, Hyatt SL, Yang HS, Soloway PD, Hanson RW, Patel MS (2001) Inactivation of the murine pyruvate dehydrogenase (Pdha1) gene and its effect on early embryonic development. Mol Genet Metab 74(3):293–302. https://doi.org/10.1006/mgme.2001.3249
75. Vanderperre B, Herzig S, Krznar P, Horl M, Ammar Z, Montessuit S, Pierredon S, Zamboni N, Martinou JC (2016) Embryonic lethality of mitochondrial pyruvate carrier 1 deficient mouse can be rescued by a ketogenic diet. PLoS Genet 12(5):e1006056. https://doi.org/10.1371/journal.pgen.1006056
76. Bowman CE, Zhao L, Hartung T, Wolfgang MJ (2016) Requirement for the mitochondrial pyruvate carrier in mammalian development revealed by a hypomorphic allelic series. Mol Cell Biol 36(15):2089–2104. https://doi.org/10.1128/MCB.00166-16
77. Ni M, Solmonson A, Pan C, Yang C, Li D, Notzon A, Cai L, Guevara G, Zacharias LG, Faubert B, Vu HS, Jiang L, Ko B, Morales NM, Pei J, Vale G, Rakheja D, Grishin NV, McDonald JG, Gotway GK, McNutt MC, Pascual JM, DeBerardinis RJ

(2019) Functional assessment of lipoyltransferase-1 deficiency in cells, mice, and humans. Cell Rep 27(5):1376-1386.e1376. https://doi.org/10.1016/j.celrep.2019.04.005
78. Muoio DM (2014) Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. Cell 159(6):1253–1262. https://doi.org/10.1016/j.cell.2014.11.034
79. Illsley NP (2000) Glucose transporters in the human placenta. Placenta 21(1):14–22. https://doi.org/10.1053/plac.1999.0448
80. Gaither K, Quraishi AN, Illsley NP (1999) Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter. J Clin Endocrinol Metab 84(2):695–701. https://doi.org/10.1210/jcem.84.2.5438
81. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet (London, England) 341(8850):938–941. https://doi.org/10.1016/0140-6736(93)91224-a
82. Desoye G, Hauguel-de Mouzon S (2007) The human placenta in gestational diabetes mellitus. The insulin and cytokine network. Diabetes Care 30(Suppl 2):S120-126. https://doi.org/10.2337/dc07-s203
83. Matsubara S, Sato I (2000) Glucose production and glucose-6-phosphatase in the human placenta. Placenta 21(5–6):591–593. https://doi.org/10.1053/plac.1999.0509
84. Leonce J, Brockton N, Robinson S, Venkatesan S, Bannister P, Raman V, Murphy K, Parker K, Pavitt D, Teoh TG, Regan L, Burchell A, Steer P, Johnston DG (2006) Glucose production in the human placenta. Placenta 27(Suppl A):S103-108. https://doi.org/10.1016/j.placenta.2006.02.006
85. Prendergast CH, Parker KH, Gray R, Venkatesan S, Bannister P, Castro-Soares J, Murphy KW, Beard RW, Regan L, Robinson S, Steer P, Halliday D, Johnston DG (1999) Glucose production by the human placenta in vivo. Placenta 20(7):591–598. https://doi.org/10.1053/plac.1999.0419
86. Akison LK, Nitert MD, Clifton VL, Moritz KM, Simmons DG (2017) Review: alterations in placental glycogen deposition in complicated pregnancies: current preclinical and clinical evidence. Placenta 54:52–58. https://doi.org/10.1016/j.placenta.2017.01.114
87. Tunster S, Watson E, Fowden A, Burton GJ (2020) Placental glycogen stores and fetal growth: insights from genetic mouse models. Reproduction. https://doi.org/10.1530/rep-20-0007
88. Meschia G, Battaglia FC, Hay WW, Sparks JW (1980) Utilization of substrates by the ovine placenta in vivo. Fed Proc 39(2):245–249
89. Owens JA, Falconer J, Robinson JS (1987) Effect of restriction of placental growth on fetal and utero-placental metabolism. J Dev Physiol 9(3):225–238
90. Sparks JW, Hay WW, Bonds D, Meschia G, Battaglia FC (1982) Simultaneous measurements of lactate turnover rate and umbilical lactate uptake in the fetal lamb. J Clin Invest 70(1):179–192
91. Markovic S, Fages A, Roussel T, Hadas R, Brandis A, Neeman M, Frydman L (2018) Placental physiology monitored by hyperpolarized dynamic (13)C magnetic resonance. Proc Natl Acad Sci USA. https://doi.org/10.1073/pnas.1715175115
92. Sferruzzi-Perri AN, Higgins JS, Vaughan OR, Murray AJ, Fowden AL (2019) Placental mitochondria adapt developmentally and in response to hypoxia to support fetal growth. Proc Natl Acad Sci USA 116(5):1621–1626. https://doi.org/10.1073/pnas.1816056116
93. Greengard O (1971) Enzymic differentiation in mammalian tissues. Essays Biochem 7:159–205
94. Novak EM, Keller BO, Innis SM (2012) Metabolic development in the liver and the implications of the n-3 fatty acid supply. Am J Physiol Gastrointest Liver Physiol 302(2):G250-259. https://doi.org/10.1152/ajpgi.00189.2011
95. Rando G, Tan CK, Khaled N, Montagner A, Leuenberger N, Bertrand-Michel J, Paramalingam E, Guillou H, Wahli W (2016) Glucocorticoid receptor-PPARalpha axis in fetal mouse liver prepares neonates for milk lipid catabolism. elife. https://doi.org/10.7554/eLife.11853
96. Fowden AL, Forhead AJ (2015) Glucocorticoids as regulatory signals during intrauterine development. Exp Physiol 100(12):1477–1487. https://doi.org/10.1113/ep085212
97. McGill-Vargas L, Gastaldelli A, Liang H, Guerra DA, Johnson-Pais T, Seidner S, McCurnin D, Muscogiuri G, DeFronzo R, Musi N, Blanco C (2017) Hepatic insulin resistance and altered gluconeogenic pathway in premature baboons. Endocrinology 158(5):1140–1151. https://doi.org/10.1210/en.2016-1806
98. Wesolowski SR, Mulligan CM, Janssen RC, Baker PR 2nd, Bergman BC, D'Alessandro A, Nemkov T, Maclean KN, Jiang H, Dean TA, Takahashi DL, Kievit P, McCurdy CE, Aagaard KM, Friedman JE (2018) Switching obese mothers to a healthy diet improves fetal hypoxemia, hepatic metabolites, and lipotoxicity in non-human primates. Mol Metab 18:25–41. https://doi.org/10.1016/j.molmet.2018.09.008
99. Cetin I, de Santis MS, Taricco E, Radaelli T, Teng C, Ronzoni S, Spada E, Milani S, Pardi G (2005) Maternal and fetal amino acid concentrations in normal pregnancies and in pregnancies with gestational diabetes mellitus. Am J Obstet Gynecol 192(2):610–617. https://doi.org/10.1016/j.ajog.2004.08.011
100. Girard JR, Ferre P, Gilbert M, Kervran A, Assan R, Marliss EB (1977) Fetal metabolic response to maternal fasting in the rat. Am J Physiol 232(5):E456-463. https://doi.org/10.1152/ajpendo.1977.232.5.E456
101. Herrera E (2000) Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. Eur J Clin Nutr 54(Suppl 1):S47-51
102. Lindsay KL, Hellmuth C, Uhl O, Buss C, Wadhwa PD, Koletzko B, Entringer S (2015) Longitudinal metabolomic profiling of amino acids and lipids across healthy pregnancy. PLoS ONE 10(12):e0145794. https://doi.org/10.1371/journal.pone.0145794
103. Jansson T (2001) Amino acid transporters in the human placenta. Pediatr Res 49(2):141–147. https://doi.org/10.1203/00006450-200102000-00003
104. Carter AM (2012) Evolution of placental function in mammals: the molecular basis of gas and nutrient transfer, hormone secretion, and immune responses. Physiol Rev 92(4):1543–1576. https://doi.org/10.1152/physrev.00040.2011
105. Lager S, Powell TL (2012) Regulation of nutrient transport across the placenta. J Pregnancy 2012:179827. https://doi.org/10.1155/2012/179827
106. Vaughan OR, Rosario FJ, Powell TL, Jansson T (2017) Regulation of placental amino acid transport and fetal growth. Prog Mol Biol Transl Sci 145:217–251. https://doi.org/10.1016/bs.pmbts.2016.12.008
107. Regnault TR, de Vrijer B, Battaglia FC (2002) Transport and metabolism of amino acids in placenta. Endocrine 19(1):23–41. https://doi.org/10.1385/endo:19:1:23
108. Panitchob N, Widdows KL, Crocker IP, Johnstone ED, Please CP, Sibley CP, Glazier JD, Lewis RM, Sengers BG (2016) Computational modelling of placental amino acid transfer as an integrated system. Biochim Biophys Acta 188(7 Pt A):1451–1461. https://doi.org/10.1016/j.bbamem.2016.03.028
109. Roos S, Powell TL, Jansson T (2009) Placental mTOR links maternal nutrient availability to fetal growth. Biochem Soc Trans 37(Pt 1):295–298. https://doi.org/10.1042/bst0370295
110. Girard JR, Guillet I, Marty J, Assan R, Marliss EB (1976) Effects of exogenous hormones and glucose on plasma levels and hepatic metabolism of amino acids in the fetus and in the newborn rat. Diabetologia 12(4):327–337. https://doi.org/10.1007/bf00420976

111. Houin SS, Rozance PJ, Brown LD, Hay WW Jr, Wilkening RB, Thorn SR (2015) Coordinated changes in hepatic amino acid metabolism and endocrine signals support hepatic glucose production during fetal hypoglycemia. Am J Physiol Endocrinol Metab 308(4):E306-314. https://doi.org/10.1152/ajpendo.00396.2014
112. Kirigiti MA, Frazee T, Bennett BJ, Arik A, Blundell P, Bader LA, Bagley JL, Frias AE, Sullivan EL, Roberts CT Jr, Kievit P (2020) Effects of pre and postnatal protein restriction on maternal and offspring metabolism in the nonhuman primate. Am J Physiol Regul Integr Comp Physiol. https://doi.org/10.1152/ajpregu.00150.2019
113. Abu-Elheiga L, Matzuk MM, Kordari P, Oh W, Shaikenov T, Gu Z, Wakil SJ (2005) Mutant mice lacking acetyl-CoA carboxylase 1 are embryonically lethal. Proc Natl Acad Sci USA 102(34):12011–12016. https://doi.org/10.1073/pnas.0505714102
114. Chirala SS, Chang H, Matzuk M, Abu-Elheiga L, Mao J, Mahon K, Finegold M, Wakil SJ (2003) Fatty acid synthesis is essential in embryonic development: fatty acid synthase null mutants and most of the heterozygotes die in utero. Proc Natl Acad Sci 100(11):6358–6363. https://doi.org/10.1073/pnas.0931394100
115. Mao J, DeMayo FJ, Li H, Abu-Elheiga L, Gu Z, Shaikenov TE, Kordari P, Chirala SS, Heird WC, Wakil SJ (2006) Liver-specific deletion of acetyl-CoA carboxylase 1 reduces hepatic triglyceride accumulation without affecting glucose homeostasis. Proc Natl Acad Sci USA 103(22):8552–8557. https://doi.org/10.1073/pnas.0603115103
116. Chakravarthy MV, Pan Z, Zhu Y, Tordjman K, Schneider JG, Coleman T, Turk J, Semenkovich CF (2005) "New" hepatic fat activates PPARalpha to maintain glucose, lipid, and cholesterol homeostasis. Cell Metab 1(5):309–322. https://doi.org/10.1016/j.cmet.2005.04.002
117. Shafrir E, Khassis S (1982) Maternal-fetal fat transport versus new fat synthesis in the pregnant diabetic rat. Diabetologia 22(2):111–117
118. Clandinin MT, Chappell JE, Heim T, Swyer PR, Chance GW (1981) Fatty acid accretion in fetal and neonatal liver: implications for fatty acid requirements. Early Hum Dev 5(1):7–14. https://doi.org/10.1016/0378-3782(81)90066-9
119. Lewis RM, Childs CE, Calder PC (2018) New perspectives on placental fatty acid transfer. Prostaglandins Leukot Essent Fatty Acids 138:24–29. https://doi.org/10.1016/j.plefa.2018.10.001
120. Elphick MC, Filshie GM, Hull D (1978) The passage of fat emulsion across the human placenta. Br J Obstet Gynaecol 85(8):610–618
121. Kety SS (1957) The general metabolism of the brain in vivo. In: Richter D (ed) Metabolism of the nervous system. Pergamon, London, pp 221–237
122. Rolfe DF, Brown GC (1997) Cellular energy utilization and molecular origin of standard metabolic rate in mammals. Physiol Rev 77(3):731–758
123. Lynen F (1957) Fatty acid metabolism. In: Richter D (ed) Metabolism of the nervous system. Pergamon, London, pp 381–395
124. Naoum HG, De Chazal RC, Eaton BM, Contractor SF (1987) Characterization and specificity of lipoprotein binding to term human placental membranes. Biochim Biophys Acta 902(2):193–199
125. Wittmaack FM, Gafvels ME, Bronner M, Matsuo H, McCrae KR, Tomaszewski JE, Robinson SL, Strickland DK, Strauss JF 3rd (1995) Localization and regulation of the human very low density lipoprotein/apolipoprotein-E receptor: trophoblast expression predicts a role for the receptor in placental lipid transport. Endocrinology 136(1):340–348. https://doi.org/10.1210/endo.136.1.7828550
126. Kaminsky S, Sibley CP, Maresh M, Thomas CR, D'Souza SW (1991) The effects of diabetes on placental lipase activity in the rat and human. Pediatr Res 30(6):541–543. https://doi.org/10.1203/00006450-199112000-00009
127. Bonet B, Brunzell JD, Gown AM, Knopp RH (1992) Metabolism of very-low-density lipoprotein triglyceride by human placental cells: the role of lipoprotein lipase. Metabolism 41(6):596–603
128. Thomas CR, Lowy C (1987) The interrelationships between circulating maternal esterified and non-esterified fatty acids in pregnant guinea pigs and their relative contributions to the fetal circulation. J Dev Physiol 9(3):203–214
129. Duttaroy AK (2009) Transport of fatty acids across the human placenta: a review. Prog Lipid Res 48(1):52–61. https://doi.org/10.1016/j.plipres.2008.11.001
130. Larque E, Demmelmair H, Berger B, Hasbargen U, Koletzko B (2003) In vivo investigation of the placental transfer of (13) C-labeled fatty acids in humans. J Lipid Res 44(1):49–55
131. Ellis JM, Bowman CE, Wolfgang MJ (2015) Metabolic and tissue-specific regulation of Acyl-CoA metabolism. PLoS ONE 10(3):e0116587. https://doi.org/10.1371/journal.pone.0116587
132. Coleman RA, Lewin TM, Van Horn CG, Gonzalez-Baró MR (2002) Do acyl-CoA synthetases regulate fatty acid entry into synthetic versus degradative pathways? J Nutr 132:2123–2126
133. Tong F, Black PN, Coleman RA, DiRusso CC (2006) Fatty acid transport by vectorial acylation in mammals: roles played by different isoforms of rat long-chain acyl-CoA synthetases. Arch Biochem Biophys 447:46–52
134. Ellis JM, Frahm JL, Li LO, Coleman RA (2010) Acyl-coenzyme A synthetases in metabolic control. Curr Opin Lipidol 21(3):212–217
135. Duttaroy AK, Crozet D, Taylor J, Gordon MJ (2003) Acyl-CoA thioesterase activity in human placental choriocarcinoma (BeWo), cells: effects of fatty acids. Prostaglandins Leukot Essent Fatty Acids 68(1):43–48
136. Wu X, Huang W, Prasad PD, Seth P, Rajan DP, Leibach FH, Chen J, Conway SJ, Ganapathy V (1999) Functional characteristics and tissue distribution pattern of organic cation transporter 2 (OCTN2), an organic cation/carnitine transporter. J Pharmacol Exp Ther 290(3):1482–1492
137. Hahn P, Skala JP, Seccombe DW, Frohlich J, Penn-Walker D, Novak M, Hynie I, Towell ME (1977) Carnitine content of blood and amniotic fluid. Pediatr Res 11(8):878–880. https://doi.org/10.1203/00006450-197708000-00003
138. Rinaldo P, Cowan TM, Matern D (2008) Acylcarnitine profile analysis. Genet Med 10(2):151–156. https://doi.org/10.1097/GIM.0b013e3181614289
139. Diamant YZ, Diamant S, Freinkel N (1980) Lipid deposition and metabolism in rat placenta during gestation. Placenta 1(4):319–325
140. Perazzolo S, Hirschmugl B, Wadsack C, Desoye G, Lewis RM, Sengers BG (2017) The influence of placental metabolism on fatty acid transfer to the fetus. J Lipid Res 58(2):443–454. https://doi.org/10.1194/jlr.P072355
141. Hay WW Jr, Sparks JW, Battaglia FC, Meschia G (1984) Maternal-fetal glucose exchange: necessity of a three-pool model. Am J Physiol 246(6 Pt 1):E528-534. https://doi.org/10.1152/ajpendo.1984.246.6.E528
142. Shekhawat P, Bennett MJ, Sadovsky Y, Nelson DM, Rakheja D, Strauss AW (2003) Human placenta metabolizes fatty acids: implications for fetal fatty acid oxidation disorders and maternal liver diseases. Am J Physiol Endocrinol Metab 284(6):E1098-1105. https://doi.org/10.1152/ajpendo.00481.2002
143. Oey NA, den Boer ME, Ruiter JP, Wanders RJ, Duran M, Waterham HR, Boer K, van der Post JA, Wijburg FA (2003) High activity of fatty acid oxidation enzymes in human placenta: implications for fetal-maternal disease. J Inherit Metab Dis 26(4):385–392

144. Pantham P, Rosario FJ, Weintraub ST, Nathanielsz PW, Powell TL, Li C, Jansson T (2016) Down-regulation of placental transport of amino acids precedes the development of intrauterine growth restriction in maternal nutrient restricted baboons. Biol Reprod 95(5):98. https://doi.org/10.1095/biolreprod.116.141085
145. Neinast M, Murashige D, Arany Z (2019) Branched chain amino acids. Annu Rev Physiol 81:139–164. https://doi.org/10.1146/annurev-physiol-020518-114455
146. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, Rochon J, Gallup D, Ilkayeva O, Wenner BR, Yancy WS Jr, Eisenson H, Musante G, Surwit RS, Millington DS, Butler MD, Svetkey LP (2009) A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 9(4):311–326. https://doi.org/10.1016/j.cmet.2009.02.002
147. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, O'Donnell CJ, Carr SA, Mootha VK, Florez JC, Souza A, Melander O, Clish CB, Gerszten RE (2011) Metabolite profiles and the risk of developing diabetes. Nat Med 17(4):448–453. https://doi.org/10.1038/nm.2307
148. Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan J, Tillin T, Schmidt AF, Imamura F, Stewart ID, Perry JR, Marney L, Koulman A, Karoly ED, Forouhi NG, Sjögren RJ, Näslund E, Zierath JR, Krook A, Savage DB, Griffin JL, Chaturvedi N, Hingorani AD, Khaw KT, Barroso I, McCarthy MI, O'Rahilly S, Wareham NJ, Langenberg C (2016) Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a Mendelian randomisation analysis. PLoS Med 13(11):e1002179. https://doi.org/10.1371/journal.pmed.1002179
149. Borengasser SJ, Baker PR 2nd, Kerns ME, Miller LV, Palacios AP, Kemp JF, Westcott JE, Morrison SD, Hernandez TL, Garces A, Figueroa L, Friedman JE, Hambidge KM, Krebs NF (2018) Preconception micronutrient supplementation reduced circulating branched chain amino acids at 12 weeks gestation in an open trial of guatemalan women who are overweight or obese. Nutrients. https://doi.org/10.3390/nu10091282
150. Burdge GC, Dunn RL, Wootton SA, Jackson AA (2002) Effect of reduced dietary protein intake on hepatic and plasma essential fatty acid concentrations in the adult female rat: effect of pregnancy and consequences for accumulation of arachidonic and docosahexaenoic acids in fetal liver and brain. Br J Nutr 88(4):379–387. https://doi.org/10.1079/bjn2002664
151. Yavin E, Lin YH, Brand A, Salem N Jr (2014) Metabolic conversion of intra-amniotically-injected deuterium-labeled essential fatty acids by fetal rats following maternal n-3 fatty acid deficiency. Biochem Biophys Acta 1841(9):1336–1344. https://doi.org/10.1016/j.bbalip.2014.06.008
152. Carnielli VP, Wattimena DJ, Luijendijk IH, Boerlage A, Degenhart HJ, Sauer PJ (1996) The very low birth weight premature infant is capable of synthesizing arachidonic and docosahexaenoic acids from linoleic and linolenic acids. Pediatr Res 40(1):169–174. https://doi.org/10.1203/00006450-199607000-00030
153. Nguyen LN, Ma D, Shui G, Wong P, Cazenave-Gassiot A, Zhang X, Wenk MR, Goh EL, Silver DL (2014) Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. Nature 509(7501):503–506. https://doi.org/10.1038/nature13241
154. Ben-Zvi A, Lacoste B, Kur E, Andreone BJ, Mayshar Y, Yan H, Gu C (2014) Mfsd2a is critical for the formation and function of the blood-brain barrier. Nature 509(7501):507–511. https://doi.org/10.1038/nature13324
155. Prieto-Sanchez MT, Ruiz-Palacios M, Blanco-Carnero JE, Pagan A, Hellmuth C, Uhl O, Peissner W, Ruiz-Alcaraz AJ, Parrilla JJ, Koletzko B, Larque E (2016) Placental MFSD2a transporter is related to decreased DHA in cord blood of women with treated gestational diabetes. Clin Nutr. https://doi.org/10.1016/j.clnu.2016.01.014
156. Chambaz J, Ravel D, Manier MC, Pepin D, Mulliez N, Bereziat G (1985) Essential fatty acids interconversion in the human fetal liver. Biol Neonate 47(3):136–140
157. Poisson JP, Dupuy RP, Sarda P, Descomps B, Narce M, Rieu D, Crastes de Paulet A (1993) Evidence that liver microsomes of human neonates desaturate essential fatty acids. Biochim Biophys Acta 1167(2):109–113
158. Salem N Jr, Wegher B, Mena P, Uauy R (1996) Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. Proc Natl Acad Sci USA 93(1):49–54
159. Pauter AM, Trattner S, Gonzalez-Bengtsson A, Talamonti E, Asadi A, Dethlefsen O, Jacobsson A (2017) Both maternal and offspring Elovl2 genotypes determine systemic DHA levels in perinatal mice. J Lipid Res 58(1):111–123. https://doi.org/10.1194/jlr.M070862
160. Boden G (1996) Fuel metabolism in pregnancy and in gestational diabetes mellitus. Obstet Gynecol Clin N Am 23(1):1–10
161. Metzger BE, Ravnikar V, Vileisis RA, Freinkel N (1982) "Accelerated starvation" and the skipped breakfast in late normal pregnancy. Lancet (London, England) 1(8272):588–592
162. Painter RC, Roseboom TJ, Bleker OP (2005) Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol 20(3):345–352. https://doi.org/10.1016/j.reprotox.2005.04.005
163. Wu L, Feng X, He A, Ding Y, Zhou X, Xu Z (2017) Prenatal exposure to the Great Chinese Famine and mid-age hypertension. PLoS ONE 12(5):e0176413. https://doi.org/10.1371/journal.pone.0176413
164. Savitri AI, Yadegari N, Bakker J, van Ewijk RJ, Grobbee DE, Painter RC, Uiterwaal CS, Roseboom TJ (2014) Ramadan fasting and newborn's birth weight in pregnant Muslim women in The Netherlands. Br J Nutr 112(9):1503–1509. https://doi.org/10.1017/s0007114514002219
165. Gur EB, Turan GA, Ince O, Karadeniz M, Tatar S, Kasap E, Sahin N, Guclu S (2015) Effect of Ramadan fasting on metabolic markers, dietary intake and abdominal fat distribution in pregnancy. Hippokratia 19(4):298–303
166. Karateke A, Kaplanoglu M, Avci F, Kurt RK, Baloglu A (2015) The effect of Ramadan fasting on fetal development. Pak J Med Sci 31(6):1295–1299. https://doi.org/10.12669/pjms.316.8562
167. Dikensoy E, Balat O, Cebesoy B, Ozkur A, Cicek H, Can G (2009) The effect of Ramadan fasting on maternal serum lipids, cortisol levels and fetal development. Arch Gynecol Obstet 279(2):119–123. https://doi.org/10.1007/s00404-008-0680-x
168. Langley-Evans SC, Phillips GJ, Benediktsson R, Gardner DS, Edwards CR, Jackson AA, Seckl JR (1996) Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. Placenta 17(2–3):169–172
169. Stettler N, Zemel BS, Kumanyika S, Stallings VA (2002) Infant weight gain and childhood overweight status in a multicenter, cohort study. Pediatrics 109(2):194–199
170. Zheng X, Wang Y, Ren W, Luo R, Zhang S, Zhang JH, Zeng Q (2012) Risk of metabolic syndrome in adults exposed to the great Chinese famine during the fetal life and early childhood. Eur J Clin Nutr 66(2):231–236. https://doi.org/10.1038/ejcn.2011.161
171. Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, Norman M (2010) Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS ONE 5(10):e13582. https://doi.org/10.1371/journal.pone.0013582
172. Li C, Lumey LH (2017) Exposure to the Chinese famine of 1959–61 in early life and long-term health conditions:

a systematic review and meta-analysis. Int J Epidemiol 46(4):1157–1170. https://doi.org/10.1093/ije/dyx013
173. Anthony RV, Scheaffer AN, Wright CD, Regnault TR (2003) Ruminant models of prenatal growth restriction. Reproduction (Cambridge, England) 61:183–194
174. Holemans K, Aerts L, Van Assche FA (2003) Fetal growth restriction and consequences for the offspring in animal models. J Soc Gynecol Investig 10(7):392–399. https://doi.org/10.1016/s1071-5576(03)00134-5
175. Lopez-Tello J, Arias-Alvarez M, Gonzalez-Bulnes A, Sferruzzi-Perri AN (2019) Models of intrauterine growth restriction and fetal programming in rabbits. Mol Reprod Dev 86(12):1781–1809. https://doi.org/10.1002/mrd.23271
176. Sferruzzi-Perri AN, Camm EJ (2016) The programming power of the placenta. Front Physiol 7:33. https://doi.org/10.3389/fphys.2016.00033
177. Coan PM, Vaughan OR, Sekita Y, Finn SL, Burton GJ, Constancia M, Fowden AL (2010) Adaptations in placental phenotype support fetal growth during undernutrition of pregnant mice. J Physiol 588(Pt 3):527–538. https://doi.org/10.1113/jphysiol.2009.181214
178. Diamant YZ, Shafrir E (1978) Placental enzymes of glycolysis, gluconeogenesis and lipogenesis in the diabetic rat and in starvation. Comparison with maternal and foetal liver. Diabetologia 15(6):481–485
179. DeSisto CL, Kim SY, Sharma AJ (2014) Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. Prev Chronic Dis 11:E104. https://doi.org/10.5888/pcd11.130415
180. American Diabetes Association (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37(Supplement 1):S81–S90. https://doi.org/10.2337/dc14-S081
181. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, Sims EA (1993) Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol 264(1 Pt 1):E60-67. https://doi.org/10.1152/ajpendo.1993.264.1.E60
182. Catalano PM, Huston L, Amini SB, Kalhan SC (1999) Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. Am J Obstet Gynecol 180(4):903–916. https://doi.org/10.1016/S0002-9378(99)70662-9
183. Barbour LA, Shao J, Qiao L, Pulawa LK, Jensen DR, Bartke A, Garrity M, Draznin B, Friedman JE (2002) Human placental growth hormone causes severe insulin resistance in transgenic mice. Am J Obstet Gynecol 186(3):512–517
184. Kalkhoff RK, Kissebah AH, Kim HJ (1978) Carbohydrate and lipid metabolism during normal pregnancy: relationship to gestational hormone action. Semin Perinatol 2(4):291–307
185. Dickens LT, Naylor RN (2018) Clinical management of women with monogenic diabetes during pregnancy. Curr DiabRep 18(3):12. https://doi.org/10.1007/s11892-018-0982-8
186. Liu J, Ghaziani TT, Wolf JL (2017) Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. Am J Gastroenterol 112(6):838–846. https://doi.org/10.1038/ajg.2017.54
187. Kurtz DM, Rinaldo P, Rhead WJ, Tian L, Millington DS, Vockley J, Hamm DA, Brix AE, Lindsey JR, Pinkert CA, O'Brien WE, Wood PA (1998) Targeted disruption of mouse long-chain acyl-CoA dehydrogenase gene reveals crucial roles for fatty acid oxidation. Proc Natl Acad Sci USA 95(26):15592–15597
188. Creanza A, Cotugno M, Mazzaccara C, Frisso G, Parenti G, Capaldo B (2018) Successful pregnancy in a young woman with multiple Acyl-CoA dehydrogenase deficiency. JIMD Rep 39:1–6. https://doi.org/10.1007/8904_2017_38
189. Camp KM, Lloyd-Puryear MA, Huntington KL (2012) Nutritional treatment for inborn errors of metabolism: indications, regulations, and availability of medical foods and dietary supplements using phenylketonuria as an example. Mol Genet Metab 107(1–2):3–9. https://doi.org/10.1016/j.ymgme.2012.07.005
190. Murphy E (2015) Medical problems in obstetrics: inherited metabolic disease. Best Pract Res Clin Obstet Gynaecol 29(5):707–720. https://doi.org/10.1016/j.bpobgyn.2015.04.006
191. Manta-Vogli PD, Schulpis KH, Dotsikas Y, Loukas YL (2020) Nutrition and medical support during pregnancy and lactation in women with inborn errors of intermediary metabolism disorders (IEMDs). J Pediatr Endocrinol Metab 33(1):5–20. https://doi.org/10.1515/jpem-2019-0048
192. Paquette A, Baloni P, Holloman A, Nigam S, Bammler T, Mao Q, Price ND (2018) Temporal transcriptomic analysis of metabolic genes in maternal organs and placenta during murine pregnancy. Biol Reprod. https://doi.org/10.1093/biolre/ioy148
193. Harris JE, Pinckard KM, Wright KR, Baer LA, Arts PJ, Abay E, Shettigar VK, Lehnig AC, Robertson B, Madaris K, Canova TJ, Sims C, Goodyear LJ, Andres A, Ziolo MT, Bode L, Stanford KI (2020) Exercise-induced 3'-sialyllactose in breast milk is a critical mediator to improve metabolic health and cardiac function in mouse offspring. Nat Metab 2(8):678–687. https://doi.org/10.1038/s42255-020-0223-8
194. Jang C, Chen L, Rabinowitz JD (2018) Metabolomics and isotope tracing. Cell 173(4):822–837. https://doi.org/10.1016/j.cell.2018.03.055
195. Gazquez A, Prieto-Sanchez MT, Blanco-Carnero JE, van Harskamp D, Perazzolo S, Oosterink JE, Demmelmair H, Schierbeek H, Sengers BG, Lewis RM, van Goudoever JB, Koletzko B, Larque E (2019) In vivo kinetic study of materno-fetal fatty acid transfer in obese and normal weight pregnant women. J Physiol 597(19):4959–4973. https://doi.org/10.1113/jp278146
196. Mu J, Slevin JC, Qu D, McCormick S, Adamson SL (2008) In vivo quantification of embryonic and placental growth during gestation in mice using micro-ultrasound. Reprod Biol Endocrinol 6:34. https://doi.org/10.1186/1477-7827-6-34
197. Burnum-Johnson KE, Baker ES, Metz TO (2017) Characterizing the lipid and metabolite changes associated with placental function and pregnancy complications using ion mobility spectrometry-mass spectrometry and mass spectrometry imaging. Placenta 60(Suppl 1):S67-s72. https://doi.org/10.1016/j.placenta.2017.03.016
198. Ferguson CN, Fowler JWM, Waxer JF, Gatti RA, Loo JA (2019) Mass spectrometry-based tissue imaging of small molecules. Adv Exp Med Biol 1140:99–109. https://doi.org/10.1007/978-3-030-15950-4_5
199. De Clercq K, Persoons E, Napso T, Luyten C, Parac-Vogt TN, Sferruzzi-Perri AN, Kerckhofs G, Vriens J (2019) High-resolution contrast-enhanced microCT reveals the true three-dimensional morphology of the murine placenta. Proc Natl Acad Sci USA 116(28):13927–13936. https://doi.org/10.1073/pnas.1902688116
200. Huang Q, Cohen MA, Alsina FC, Devlin G, Garrett A, McKey J, Havlik P, Rakhilin N, Wang E, Xiang K, Mathews P, Wang L, Bock C, Ruthig V, Wang Y, Negrete M, Wong CW, Murthy PKL, Zhang S, Daniel AR, Kirsch DG, Kang Y, Capel B, Asokan A, Silver DL, Jaenisch R, Shen X (2020) Intravital imaging of mouse embryos. Science 368(6487):181–186. https://doi.org/10.1126/science.aba0210
201. Michelsen TM, Holme AM, Henriksen T (2017) Transplacental nutrient transfer in the human in vivo determined by 4 vessel sampling. Placenta 59(Suppl 1):S26-s31. https://doi.org/10.1016/j.placenta.2017.03.014
202. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, Lowe LP, Trimble ER, Coustan DR,

Hadden DR, Persson B, Hod M, Oats JJ (2012) The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 35(4):780–786. https://doi.org/10.2337/dc11-1790

203. Stuebe AM, Landon MB, Lai Y, Spong CY, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Sciscione A, Catalano P, Harper M, Saade G, Sorokin Y, Peaceman AM, Tolosa JE (2012) Maternal BMI, glucose tolerance, and adverse pregnancy outcomes. Am J Obstet Gynecol 207(1):62.e61-67. https://doi.org/10.1016/j.ajog.2012.04.035
204. Scholtens DM, Muehlbauer MJ, Daya NR, Stevens RD, Dyer AR, Lowe LP, Metzger BE, Newgard CB, Bain JR, Lowe WL Jr (2014) Metabolomics reveals broad-scale metabolic perturbations in hyperglycemic mothers during pregnancy. Diabetes Care 37(1):158–166. https://doi.org/10.2337/dc13-0989
205. Scholtens DM, Bain JR, Reisetter AC, Muehlbauer MJ, Nodzenski M, Stevens RD, Ilkayeva O, Lowe LP, Metzger BE, Newgard CB, Lowe WL Jr (2016) Metabolic networks and metabolites underlie associations between maternal glucose during pregnancy and newborn size at birth. Diabetes 65(7):2039–2050. https://doi.org/10.2337/db15-1748
206. Jacob S, Nodzenski M, Reisetter AC, Bain JR, Muehlbauer MJ, Stevens RD, Ilkayeva OR, Lowe LP, Metzger BE, Newgard CB, Scholtens DM, Lowe WL Jr (2017) Targeted metabolomics demonstrates distinct and overlapping maternal metabolites associated with BMI, glucose, and insulin sensitivity during pregnancy across four ancestry groups. Diabetes Care 40(7):911–919. https://doi.org/10.2337/dc16-2453
207. Lowe WL Jr, Bain JR, Nodzenski M, Reisetter AC, Muehlbauer MJ, Stevens RD, Ilkayeva OR, Lowe LP, Metzger BE, Newgard CB, Scholtens DM (2017) Maternal BMI and glycemia impact the fetal metabolome. Diabetes Care 40(7):902–910. https://doi.org/10.2337/dc16-2452
208. Sandler V, Reisetter AC, Bain JR, Muehlbauer MJ, Nodzenski M, Stevens RD, Ilkayeva O, Lowe LP, Metzger BE, Newgard CB, Scholtens DM, Lowe WL Jr (2017) Associations of maternal BMI and insulin resistance with the maternal metabolome and newborn outcomes. Diabetologia 60(3):518–530. https://doi.org/10.1007/s00125-016-4182-2
209. Kadakia R, Nodzenski M, Talbot O, Kuang A, Bain JR, Muehlbauer MJ, Stevens RD, Ilkayeva OR, O'Neal SK, Lowe LP, Metzger BE, Newgard CB, Scholtens DM, Lowe WL Jr (2018) Maternal metabolites during pregnancy are associated with newborn outcomes and hyperinsulinaemia across ancestries. Diabetologia. https://doi.org/10.1007/s00125-018-4781-1
210. Kadakia R, Talbot O, Kuang A, Bain JR, Muehlbauer MJ, Stevens RD, Ilkayeva OR, Lowe LP, Metzger BE, Newgard CB, Scholtens DM, Lowe WL (2019) Cord blood metabolomics: association with newborn anthropometrics and C-peptide across ancestries. J Clin Endocrinol Metab 104(10):4459–4472. https://doi.org/10.1210/jc.2019-00238
211. Sovio U, Goulding N, McBride N, Cook E, Gaccioli F, Charnock-Jones DS, Lawlor DA, Smith GCS (2020) A maternal serum metabolite ratio predicts fetal growth restriction at term. Nat Med 26(3):348–353. https://doi.org/10.1038/s41591-020-0804-9
212. Aghaeepour N, Lehallier B, Baca Q, Ganio EA, Wong RJ, Ghaemi MS, Culos A, El-Sayed YY, Blumenfeld YJ, Druzin ML, Winn VD, Gibbs RS, Tibshirani R, Shaw GM, Stevenson DK, Gaudilliere B, Angst MS (2018) A proteomic clock of human pregnancy. Am J Obstet Gynecol 218(3):347.e341-347.e314. https://doi.org/10.1016/j.ajog.2017.12.208
213. Erez O, Romero R, Maymon E, Chaemsaithong P, Done B, Pacora P, Panaitescu B, Chaiworapongsa T, Hassan SS, Tarca AL (2017) The prediction of late-onset preeclampsia: results from a longitudinal proteomics study. PLoS ONE 12(7):e0181468. https://doi.org/10.1371/journal.pone.0181468
214. Tarca AL, Romero R, Benshalom-Tirosh N, Than NG, Gudicha DW, Done B, Pacora P, Chaiworapongsa T, Panaitescu B, Tirosh D, Gomez-Lopez N, Draghici S, Hassan SS, Erez O (2019) The prediction of early preeclampsia: results from a longitudinal proteomics study. PLoS ONE 14(6):e0217273. https://doi.org/10.1371/journal.pone.0217273
215. Romero R, Erez O, Maymon E, Chaemsaithong P, Xu Z, Pacora P, Chaiworapongsa T, Done B, Hassan SS, Tarca AL (2017) The maternal plasma proteome changes as a function of gestational age in normal pregnancy: a longitudinal study. Am J Obstet Gynecol 217(1):67.e61-67.e21. https://doi.org/10.1016/j.ajog.2017.02.037
216. Paquette AG, Hood L, Price ND, Sadovsky Y (2020) Deep phenotyping during pregnancy for predictive and preventive medicine. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aay1059
217. Mitchell MD, Peiris HN, Kobayashi M, Koh YQ, Duncombe G, Illanes SE, Rice GE, Salomon C (2015) Placental exosomes in normal and complicated pregnancy. Am J Obstet Gynecol 213(4 Suppl):S173-181. https://doi.org/10.1016/j.ajog.2015.07.001
218. Tong M, Chamley LW (2015) Placental extracellular vesicles and feto-maternal communication. Cold Spring Harbor Perspect Med 5(3):a023028. https://doi.org/10.1101/cshperspect.a023028
219. Mincheva-Nilsson L, Baranov V (2010) The role of placental exosomes in reproduction. Am J Reprod Immunol (New York, NY: 1989) 63(6):520–533. https://doi.org/10.1111/j.1600-0897.2010.00822.x
220. Luo SS, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, Mishima T, Takizawa T, Shigihara T, Goto T, Izumi A, Ohkuchi A, Matsubara S, Takeshita T, Takizawa T (2009) Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. Biol Reprod 81(4):717–729. https://doi.org/10.1095/biolreprod.108.075481
221. Dumont TMF, Mouillet JF, Bayer A, Gardner CL, Klimstra WB, Wolf DG, Yagel S, Balmir F, Binstock A, Sanfilippo JS, Coyne CB, Larkin JC, Sadovsky Y (2017) The expression level of C19MC miRNAs in early pregnancy and in response to viral infection. Placenta 53:23–29. https://doi.org/10.1016/j.placenta.2017.03.011
222. Record M (2014) Intercellular communication by exosomes in placenta: a possible role in cell fusion? Placenta 35(5):297–302. https://doi.org/10.1016/j.placenta.2014.02.009
223. Jayabalan N, Nair S, Nuzhat Z, Rice GE, Zuniga FA, Sobrevia L, Leiva A, Sanhueza C, Gutierrez JA, Lappas M, Freeman DJ, Salomon C (2017) Cross talk between adipose tissue and placenta in obese and gestational diabetes mellitus pregnancies via exosomes. Front Endocrinol (Lausanne) 8:239. https://doi.org/10.3389/fendo.2017.00239
224. Tong M, Chen Q, James JL, Wise MR, Stone PR, Chamley LW (2017) In vivo targets of human placental micro-vesicles vary with exposure time and pregnancy. Reproduction 153(6):835–845. https://doi.org/10.1530/rep-16-0615
225. James-Allan LB, Rosario FJ, Barner K, Lai A, Guanzon D, McIntyre HD, Lappas M, Powell TL, Salomon C, Jansson T (2020) Regulation of glucose homeostasis by small extracellular vesicles in normal pregnancy and in gestational diabetes. FASEB J 34(4):5724–5739. https://doi.org/10.1096/fj.201902522RR
226. Adam S, Elfeky O, Kinhal V, Dutta S, Lai A, Jayabalan N, Nuzhat Z, Palma C, Rice GE, Salomon C (2017) Review: fetal-maternal communication via extracellular vesicles—implications for complications of pregnancies. Placenta 54:83–88. https://doi.org/10.1016/j.placenta.2016.12.001
227. Paquette AG, Chu T, Wu X, Wang K, Price ND, Sadovsky Y (2018) Distinct communication patterns of trophoblastic miRNA among the maternal-placental-fetal compartments. Placenta 72–73:28–35. https://doi.org/10.1016/j.placenta.2018.10.004

228. Zempleni J, Aguilar-Lozano A, Sadri M, Sukreet S, Manca S, Wu D, Zhou F, Mutai E (2017) Biological activities of extracellular vesicles and their cargos from bovine and human milk in humans and implications for infants. J Nutr 147(1):3–10. https://doi.org/10.3945/jn.116.238949
229. Aghaeepour N, Ganio EA, McIlwain D, Tsai AS, Tingle M, Van Gassen S, Gaudilliere DK, Baca Q, McNeil L, Okada R, Ghaemi MS, Furman D, Wong RJ, Winn VD, Druzin ML, El-Sayed YY, Quaintance C, Gibbs R, Darmstadt GL, Shaw GM, Stevenson DK, Tibshirani R, Nolan GP, Lewis DB, Angst MS, Gaudilliere B (2017) An immune clock of human pregnancy. Sci Immunol. https://doi.org/10.1126/sciimmunol.aan2946
230. Gomez-Lopez N, Romero R, Hassan SS, Bhatti G, Berry SM, Kusanovic JP, Pacora P, Tarca AL (2019) The cellular transcriptome in the maternal circulation during normal pregnancy: a longitudinal study. Front Immunol 10:2863. https://doi.org/10.3389/fimmu.2019.02863
231. Vossaert L, Wang Q, Salman R, McCombs AK, Patel V, Qu C, Mancini MA, Edwards DP, Malovannaya A, Liu P, Shaw CA, Levy B, Wapner RJ, Bi W, Breman AM, Van den Veyver IB, Beaudet AL (2019) Validation studies for single circulating trophoblast genetic testing as a form of noninvasive prenatal diagnosis. Am J Hum Genet 105(6):1262–1273. https://doi.org/10.1016/j.ajhg.2019.11.004
232. Bianchi DW, Chiu RWK (2018) Sequencing of circulating cell-free DNA during pregnancy. N Engl J Med 379(5):464–473. https://doi.org/10.1056/NEJMra1705345
233. Breveglieri G, D'Aversa E, Finotti A, Borgatti M (2019) Non-invasive prenatal testing using fetal DNA. Mol Diagn Ther 23(2):291–299. https://doi.org/10.1007/s40291-019-00385-2
234. Ngo TTM, Moufarrej MN, Rasmussen MH, Camunas-Soler J, Pan W, Okamoto J, Neff NF, Liu K, Wong RJ, Downes K, Tibshirani R, Shaw GM, Skotte L, Stevenson DK, Biggio JR, Elovitz MA, Melbye M, Quake SR (2018) Noninvasive blood tests for fetal development predict gestational age and preterm delivery. Science 360(6393):1133–1136. https://doi.org/10.1126/science.aar3819
235. Kara RJ, Bolli P, Karakikes I, Matsunaga I, Tripodi J, Tanweer O, Altman P, Shachter NS, Nakano A, Najfeld V, Chaudhry HW (2012) Fetal cells traffic to injured maternal myocardium and undergo cardiac differentiation. Circ Res 110(1):82–93. https://doi.org/10.1161/circresaha.111.249037
236. Vadakke-Madathil S, LaRocca G, Raedschelders K, Yoon J, Parker SJ, Tripodi J, Najfeld V, Van Eyk JE, Chaudhry HW (2019) Multipotent fetal-derived Cdx2 cells from placenta regenerate the heart. Proc Natl Acad Sci USA 116(24):11786–11795. https://doi.org/10.1073/pnas.1811827116
237. Fugazzola L, Cirello V, Beck-Peccoz P (2011) Fetal microchimerism as an explanation of disease. Nat Rev Endocrinol 7(2):89–97. https://doi.org/10.1038/nrendo.2010.216
238. Boddy AM, Fortunato A, Wilson Sayres M, Aktipis A (2015) Fetal microchimerism and maternal health: a review and evolutionary analysis of cooperation and conflict beyond the womb. BioEssays 37(10):1106–1118. https://doi.org/10.1002/bies.201500059
239. Kinder JM, Stelzer IA, Arck PC, Way SS (2017) Immunological implications of pregnancy-induced microchimerism. Nat Rev Immunol 17(8):483–494. https://doi.org/10.1038/nri.2017.38
240. Handelman SK, Romero R, Tarca AL, Pacora P, Ingram B, Maymon E, Chaiworapongsa T, Hassan SS, Erez O (2019) The plasma metabolome of women in early pregnancy differs from that of non-pregnant women. PLoS ONE 14(11):e0224682. https://doi.org/10.1371/journal.pone.0224682
241. Pinto J, Barros AS, Domingues MR, Goodfellow BJ, Galhano E, Pita C, Almeida Mdo C, Carreira IM, Gil AM (2015) Following healthy pregnancy by NMR metabolomics of plasma and correlation to urine. J Proteome Res 14(2):1263–1274. https://doi.org/10.1021/pr5011982
242. Orczyk-Pawilowicz M, Jawien E, Deja S, Hirnle L, Zabek A, Mlynarz P (2016) Metabolomics of human amniotic fluid and maternal plasma during normal pregnancy. PLoS ONE 11(4):e0152740. https://doi.org/10.1371/journal.pone.0152740
243. Wang Q, Wurtz P, Auro K, Makinen VP, Kangas AJ, Soininen P, Tiainen M, Tynkkynen T, Jokelainen J, Santalahti K, Salmi M, Blankenberg S, Zeller T, Viikari J, Kahonen M, Lehtimaki T, Salomaa V, Perola M, Jalkanen S, Jarvelin MR, Raitakari OT, Kettunen J, Lawlor DA, Ala-Korpela M (2016) Metabolic profiling of pregnancy: cross-sectional and longitudinal evidence. BMC Med 14(1):205. https://doi.org/10.1186/s12916-016-0733-0
244. Voerman E, Jaddoe VWV, Uhl O, Shokry E, Horak J, Felix JF, Koletzko B, Gaillard R (2020) A population-based resource for intergenerational metabolomics analyses in pregnant women and their children: the generation R study. Metabolomics 16(4):43. https://doi.org/10.1007/s11306-020-01667-1
245. Zhao H, Li H, Chung ACK, Xiang L, Li X, Zheng Y, Luan H, Zhu L, Liu W, Peng Y, Zhao Y, Xu S, Li Y, Cai Z (2018) Large-scale longitudinal metabolomics study reveals different trimester-specific alterations of metabolites in relation to gestational diabetes mellitus. J Proteome Res. https://doi.org/10.1021/acs.jproteome.8b00602
246. Heazell AE, Bernatavicius G, Warrander L, Brown MC, Dunn WB (2012) A metabolomic approach identifies differences in maternal serum in third trimester pregnancies that end in poor perinatal outcome. Reprod Sci (Thousand Oaks, Calif) 19(8):863–875. https://doi.org/10.1177/1933719112438446
247. Dunn WB, Brown M, Worton SA, Davies K, Jones RL, Kell DB, Heazell AEP (2011) The metabolome of human placental tissue: investigation of first trimester tissue and changes related to preeclampsia in late pregnancy. Metabolomics 8(4):579–597. https://doi.org/10.1007/s11306-011-0348-6
248. Troisi J, Landolfi A, Sarno L, Richards S, Symes S, Adair D, Ciccone C, Scala G, Martinelli P, Guida M (2018) A metabolomics-based approach for non-invasive screening of fetal central nervous system anomalies. Metabolomics 14(6):77. https://doi.org/10.1007/s11306-018-1370-8
249. Favretto D, Cosmi E, Ragazzi E, Visentin S, Tucci M, Fais P, Cecchetto G, Zanardo V, Viel G, Ferrara SD (2012) Cord blood metabolomic profiling in intrauterine growth restriction. Anal Bioanal Chem 402(3):1109–1121. https://doi.org/10.1007/s00216-011-5540-z
250. Alexandre-Gouabau MC, Courant F, Moyon T, Kuster A, Le Gall G, Tea I, Antignac JP, Darmaun D (2013) Maternal and cord blood LC-HRMS metabolomics reveal alterations in energy and polyamine metabolism, and oxidative stress in very-low birth weight infants. J Proteome Res 12(6):2764–2778. https://doi.org/10.1021/pr400122v
251. Miranda J, Simoes RV, Paules C, Canueto D, Pardo-Cea MA, Garcia-Martin ML, Crovetto F, Fuertes-Martin R, Domenech M, Gomez-Roig MD, Eixarch E, Estruch R, Hansson SR, Amigo N, Canellas N, Crispi F, Gratacos E (2018) Metabolic profiling and targeted lipidomics reveals a disturbed lipid profile in mothers and fetuses with intrauterine growth restriction. Sci Rep 8(1):13614. https://doi.org/10.1038/s41598-018-31832-5
252. Chen Q, Francis E, Hu G, Chen L (2018) Metabolomic profiling of women with gestational diabetes mellitus and their offspring: review of metabolomics studies. J Diabetes Complicat 32(5):512–523. https://doi.org/10.1016/j.jdiacomp.2018.01.007
253. Bentley-Lewis R, Huynh J, Xiong G, Lee H, Wenger J, Clish C, Nathan D, Thadhani R, Gerszten R (2015) Metabolomic profiling in the prediction of gestational diabetes mellitus. Diabetologia 58(6):1329–1332. https://doi.org/10.1007/s00125-015-3553-4

254. Mokkala K, Vahlberg T, Pellonpera O, Houttu N, Koivuniemi E, Laitinen K (2020) Distinct metabolic profile in early pregnancy of overweight and obese women developing gestational diabetes. J Nutr 150(1):31–37. https://doi.org/10.1093/jn/nxz220
255. Liu T, Li J, Xu F, Wang M, Ding S, Xu H, Dong F (2016) Comprehensive analysis of serum metabolites in gestational diabetes mellitus by UPLC/Q-TOF-MS. Anal Bioanal Chem 408(4):1125–1135. https://doi.org/10.1007/s00216-015-9211-3
256. White SL, Pasupathy D, Sattar N, Nelson SM, Lawlor DA, Briley AL, Seed PT, Welsh P, Poston L (2017) Metabolic profiling of gestational diabetes in obese women during pregnancy. Diabetologia 60(10):1903–1912. https://doi.org/10.1007/s00125-017-4380-6
257. Huhtala MS, Tertti K, Pellonpera O, Ronnemaa T (2018) Amino acid profile in women with gestational diabetes mellitus treated with metformin or insulin. Diabetes Res Clin Pract 146:8–17. https://doi.org/10.1016/j.diabres.2018.09.014
258. Lu YP, Reichetzeder C, Prehn C, von Websky K, Slowinski T, Chen YP, Yin LH, Kleuser B, Yang XS, Adamski J, Hocher B (2018) Fetal serum metabolites are independently associated with gestational diabetes mellitus. Cell Physiol Biochem 45(2):625–638. https://doi.org/10.1159/000487119
259. Ortega-Senovilla H, Schaefer-Graf U, Herrera E (2019) Pregnant women with gestational diabetes and with well controlled glucose levels have decreased concentrations of individual fatty acids in maternal and cord serum. Diabetologia. https://doi.org/10.1007/s00125-019-05054-x
260. Gelaye B, Clish CB, Denis M, Larrabure G, Tadesse MG, Deik A, Pierce K, Bullock K, Dennis C, Enquobahrie DA, Williams MA (2018) Metabolomics signatures associated with an oral glucose challenge in pregnant women. Diabetes Metab. https://doi.org/10.1016/j.diabet.2018.01.004
261. Hellmuth C, Lindsay KL, Uhl O, Buss C, Wadhwa PD, Koletzko B, Entringer S (2019) Maternal metabolomic profile and fetal programming of offspring adiposity: identification of potentially protective lipid metabolites. Mol Nutr Food Res 63(1):e1700889. https://doi.org/10.1002/mnfr.201700889
262. Fotiou M, Fotakis C, Tsakoumaki F, Athanasiadou E, Kyrkou C, Dimitropoulou A, Tsiaka T, Chatziioannou AC, Sarafidis K, Menexes G, Theodoridis G, Biliaderis CG, Zoumpoulakis P, Athanasiadis AP, Michaelidou AM (2018) (1)H NMR-based metabolomics reveals the effect of maternal habitual dietary patterns on human amniotic fluid profile. Sci Rep 8(1):4076. https://doi.org/10.1038/s41598-018-22230-y
263. Cai X, Liang N, Wang H, Gao A, Xiao R, Yu H (2020) Lipidomic profiles of maternal blood at the earlier stage of gestation and umbilical venous blood in response to supraphysiological hypercholesterolemia versus physiological hypercholesterolemia: an evidence of potential biomarkers and early intervention. Biochim Biophys Acta 1865(3):158587. https://doi.org/10.1016/j.bbalip.2019.158587
264. Austdal M, Skrastad RB, Gundersen AS, Austgulen R, Iversen AC, Bathen TF (2014) Metabolomic biomarkers in serum and urine in women with preeclampsia. PLoS ONE 9(3):e91923. https://doi.org/10.1371/journal.pone.0091923
265. Austdal M, Tangeras LH, Skrastad RB, Salvesen K, Austgulen R, Iversen AC, Bathen TF (2015) First trimester urine and serum metabolomics for prediction of preeclampsia and gestational hypertension: a prospective screening study. Int J Mol Sci 16(9):21520–21538. https://doi.org/10.3390/ijms160921520
266. Koster MP, Vreeken RJ, Harms AC, Dane AD, Kuc S, Schielen PC, Hankemeier T, Berger R, Visser GH, Pennings JL (2015) First-trimester serum acylcarnitine levels to predict preeclampsia: a metabolomics approach. Dis Mark 2015:857108. https://doi.org/10.1155/2015/857108
267. Bahado-Singh RO, Syngelaki A, Mandal R, Graham SF, Akolekar R, Han B, Bjondahl TC, Dong E, Bauer S, Alpay-Savasan Z, Turkoglu O, Ogunyemi D, Poon LC, Wishart DS, Nicolaides KH (2017) Metabolomic determination of pathogenesis of late-onset preeclampsia. J Matern Fetal Neonatal Med 30(6):658–664. https://doi.org/10.1080/14767058.2016.1185411
268. Powell KL, Carrozzi A, Stephens AS, Tasevski V, Morris JM, Ashton AW, Dona AC (2018) Utility of metabolic profiling of serum in the diagnosis of pregnancy complications. Placenta 66:65–73. https://doi.org/10.1016/j.placenta.2018.04.005
269. Austdal M, Thomsen LC, Tangeras LH, Skei B, Mathew S, Bjorge L, Austgulen R, Bathen TF, Iversen AC (2015) Metabolic profiles of placenta in preeclampsia using HR-MAS MRS metabolomics. Placenta 36(12):1455–1462. https://doi.org/10.1016/j.placenta.2015.10.019
270. Li X, Yin M, Gu J, Hou Y, Tian F, Sun F (2018) Metabolomic profiling of plasma samples from women with recurrent spontaneous abortion. Med Sci Monit 24:4038–4045. https://doi.org/10.12659/msm.907653
271. Hellmuth C, Uhl O, Kirchberg FF, Harder U, Peissner W, Koletzko B, Nathanielsz PW (2016) Influence of moderate maternal nutrition restriction on the fetal baboon metabolome at 0.5 and 0.9 gestation. Nutr Metab Cardiovasc Dis 26(9):786–796. https://doi.org/10.1016/j.numecd.2016.04.004
272. Beckstrom AC, Tanya P, Humston EM, Snyder LR, Synovec RE, Juul SE (2012) The perinatal transition of the circulating metabolome in a nonhuman primate. Pediatr Res 71(4 Pt 1):338–344. https://doi.org/10.1038/pr.2011.74
273. Walejko JM, Antolic A, Koelmel JP, Garrett TJ, Edison AS, Keller-Wood M (2019) Chronic maternal cortisol excess during late gestation leads to metabolic alterations in the newborn heart. Am J Physiol Endocrinol Metab. https://doi.org/10.1152/ajpendo.00386.2018
274. Lin G, Liu C, Feng C, Fan Z, Dai Z, Lai C, Li Z, Wu G, Wang J (2012) Metabolomic analysis reveals differences in umbilical vein plasma metabolites between normal and growth-restricted fetal pigs during late gestation. J Nutr 142(6):990–998. https://doi.org/10.3945/jn.111.153411
275. Stuart TJ, O'Neill K, Condon D, Sasson I, Sen P, Xia Y, Simmons RA (2018) Diet-induced obesity alters the maternal metabolome and early placenta transcriptome and decreases placenta vascularity in the mouse. Biol Reprod 98(6):795–809. https://doi.org/10.1093/biolre/ioy010
276. Matoba S, Nakamuta S, Miura K, Hirose M, Shiura H, Kohda T, Nakamuta N, Ogura A (2019) Paternal knockout of Slc38a4/SNAT4 causes placental hypoplasia associated with intrauterine growth restriction in mice. Proc Natl Acad Sci USA 116(42):21047–21053. https://doi.org/10.1073/pnas.1907884116
277. Nishimura T, Higuchi K, Sai Y, Sugita Y, Yoshida Y, Tomi M, Wada M, Wakayama T, Tamura A, Tsukita S, Soga T, Nakashima E (2014) Fetal growth retardation and lack of hypotaurine in ezrin knockout mice. PLoS ONE 9(8):e105423. https://doi.org/10.1371/journal.pone.0105423
278. Stanley JL, Sulek K, Andersson IJ, Davidge ST, Kenny LC, Sibley CP, Mandal R, Wishart DS, Broadhurst DI, Baker PN (2015) Sildenafil therapy normalizes the aberrant metabolomic profile in the Comt(−/−) mouse model of preeclampsia/fetal growth restriction. Sci Rep 5:18241. https://doi.org/10.1038/srep18241
279. Lian S, Li W, Wang D, Xu B, Guo X, Yang H, Wang J (2020) Effects of prenatal cold stress on maternal serum metabolomics in rats. Life Sci 246:117432. https://doi.org/10.1016/j.lfs.2020.117432

280. Kimura I, Miyamoto J, Ohue-Kitano R, Watanabe K, Yamada T, Onuki M, Aoki R, Isobe Y, Kashihara D, Inoue D, Inaba A, Takamura Y, Taira S, Kumaki S, Watanabe M, Ito M, Nakagawa F, Irie J, Kakuta H, Shinohara M, Iwatsuki K, Tsujimoto G, Ohno H, Arita M, Itoh H, Hase K (2020) Maternal gut microbiota in pregnancy influences offspring metabolic phenotype in mice. Science 367(6481):eaaw8429. https://doi.org/10.1126/science.aaw8429

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.